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(54) Title: ORAL HYPOGLYCEMIC AGENTS

(57) Abstract

Antihyperglycemic compounds selected from the group consisting of C-substituted pentacycloazoles and N-alkyl-substituted pentacycloazoles.

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Title

ORAL HYPOGLYCEMIC AGENTS

Background of the Invention

This invention relates to C-substituted pentacycloazoles containing heteroatoms in the 2, 3 and 5 positions of the pentacycloazole ring and N-substituted pentacycloazoles containing nitrogen atoms in either the 2 and 4 positions or in the 3 position of the pentacycloazole ring.

Ellingboe *et al.* state in the J. Med. Chem., Vol. 36, pages 2485-2493 (1993), which is hereby incorporated by reference, that drugs currently available for the control of the hyperglycemia associated with type 2 (non-insulin dependent) diabetes mellitus possess significant liabilities or efficacy limitations and that considerable effort has been directed toward the development of novel, orally active antihyperglycemic drugs. They also state that many of these new compounds incorporate a relatively acidic heterocycle which serves as the pharmacophore responsible for antihyperglycemic activity, such as thiazolidine-2,4-dione, tetrazole and oxazolidine-2,4-dione rings. In an earlier paper, J. Med. Chem. Vol. 35, pages 1176-1183 (1992), which is hereby incorporated by reference, Ellingboe *et al.*

described a number of antihyperglycemic agents, which contain an acidic 3H-1,2,3,5-oxathiadiazole 2-oxide ring, appended via a methylene bridge to numerous aromatic systems. Kangi et al. E.P. 177, 353, which is hereby incorporated by reference, discloses antihyperglycemic thiazolidine pharmacophore appended via a methylene bridge to suitable aromatic systems.

The general object of this invention is to provide new antihyperglycemic compounds based on new pharmacophores. Other objects appear hereinafter.

In one aspect, this invention is an antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 position of the pentacycloazole ring and N-substituted pentacycloazole pharmacophore containing nitrogen atoms in a position selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3 position of the pentacycloazole ring.

In a second aspect, this invention is an antihyperglycemic composition comprising a pharmaceutically acceptable carrier, diluent or excipient and an effective amount of an antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 position of the pentacycloazole ring and N-alkyl substituted pentacycloazole pharmacophore containing nitrogen or other hetero atoms in a position selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3 position of the pentacycloazole ring.

In a third aspect, this invention is a method of reducing the hyperglycemia associated with non-insulin dependent diabetes mellitus which method comprises orally administering to a mammal, such as a human, a therapeutic

dose of an antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 position of the pentacycloazole ring and N-substituted pentacycloazole pharmacophore containing nitrogen atoms in a position selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3 position of the pentacycloazole ring.

We have now found that the objects of this invention can be attained with antihyperglycemic compounds having a C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2, 3 and 5 position of the pentacycloazole ring or an N-alkyl-substituted pentacycloazole pharmacophore (where the alkyl group has 1 to 12 carbon atoms) containing nitrogen atoms in both the 2 and 4 positions or in the 3 position of the pentacycloazole ring wherein the pentacycloazole ring is linked to a suitable aromatic system utilized with pharmacophores responsible for antihyperglycemic activity by an aliphatic group of 1 to 2 carbon atoms and a carbon atom of said aliphatic group is bonded directly to the pentacycloazole ring. Our studies have shown that other things being equal, many other compounds containing different pentacycloazole moieties, lack the antihyperglycemic activity of the compounds of this invention. Further, it appears that if the pentacycloazole moiety is linked to the same aromatic system by an isomeric aliphatic group having no carbon atom bonded to the pentacycloazole ring, the compound lacks antihyperglycemic activity. For example, when a $-CH_2-S-$ linker was employed, the compound was inactive when the "S-" part of the linker was bonded to a C-pentacycloazole moiety and active when the "CH_2-" part of the linker was bonded to a C-pentacycloazole moiety. Likewise, when the pharmacophore was bonded directly

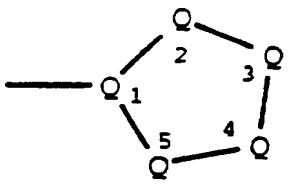
to the aromatic moiety without an aliphatic linking group, the compounds were inactive.

While Mullican *et al.* in the J. Med. Chem., Vol. 36, pages 1090-1099 (1993) disclose a C-substituted-2,3,5-triazole linked through methylene to a 4-hydroxy-3,5-dibutylphenyl moiety at page 1091 and Boschelli et al. in J. Med. Chem., Vol. 36, pages 1802 to 1810 (1993) disclose a C-substituted pentacycloazole containing heteroatoms in the 2,3 and 5 position linked through methylene to a dichlorophenylaminophenyl group moiety at page 1804, neither article describes or suggests that the compounds have antihyperglycemic activity. Further, to the best of our knowledge neither the 4-hydroxy-3,5-dibutylphenyl moiety nor the dichlorophenylaminophenyl group have been used with pharmacophores responsible for antihyperglycemic activity.

The compounds of this invention can be represented by the structure

$$Ar-(G)_{n-1}-(CH_2)_{m-1}-CH_2Z$$

The bond of attachment to Z is assigned number 1 as described in the following schematic structure formula (I):

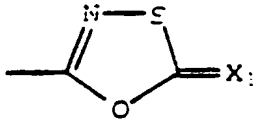


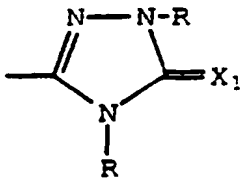
(I)

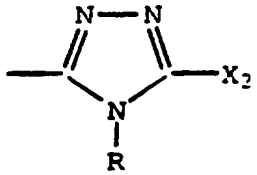
where each Q is independently C, N, O, or S as described in the following definition of Z.

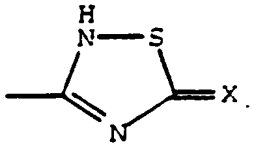
Z is a C-substituted pentacycloazole containing heteroatoms in the 2, 3 and 5 positions of the pentacycloazole ring or an N-substituted (N at position 1) pentacycloazole containing N atoms in either the 2 and 4 positions or in the 3 position of the pentacycloazole ring; G is oxygen or sulfur; m and n are whole numbers ranging from 1 to 2; and Ar is a suitable aromatic system.

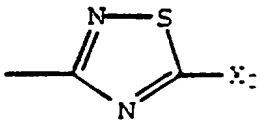
In somewhat greater detail, Z can have any of the structures inclusive of double bond tautomeric forms as follows:

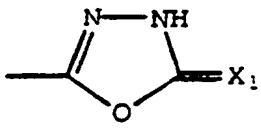


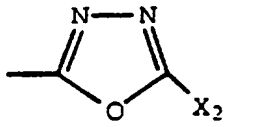


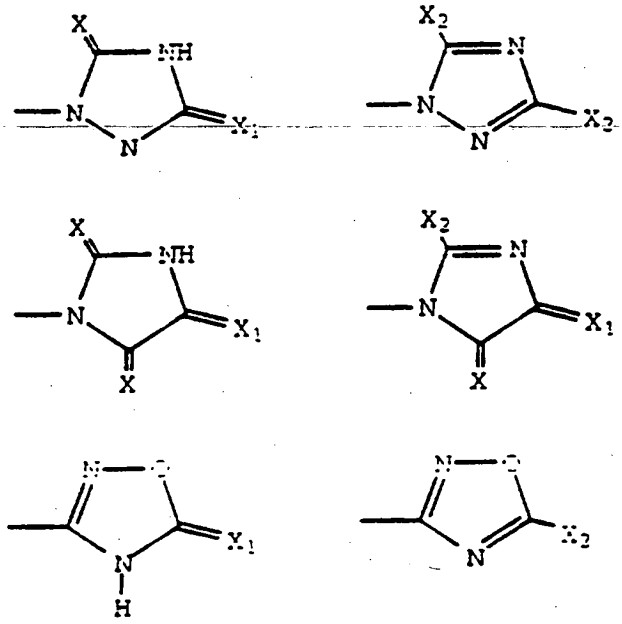












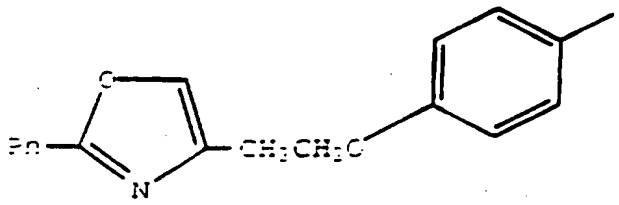
wherein X_1 is O or S; X_2 is -SR; and each R is independently selected from H, methyl, ethyl, propyl and butyl.

Ar can be any suitable aromatic system utilized with other pharmacophores responsible for antihyperglycemic activity such as those disclosed in the aforesaid Ellingboe *et al.* articles; the aforesaid Kangi *et al.* E.P. 177, 353; Momose *et al.* in Chem. Pharm. Bull., Vol. 39, No. 6 at pages 1440 to 1445 (1991); Cantello *et al.* E.P. 415605; Clark *et al.* U.S. 4,791,125; Kees U.S. 5,183,825; Goldstein *et al.* WO 93/00343; Hindley E.P. 306,228 all of which are hereby incorporated by reference. Accordingly, the aromatic systems can range from simple dihydronaphthalene moieties in U.S. 5,183,825 to aromatic rings linked to heterocylic rings.

The preferred aromatic systems can be represented by the structure:

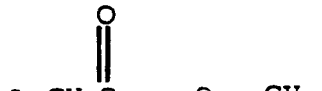
$$Y-(CH_2)_p-(G')-Ar'-$$

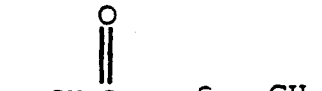
wherein Ar' is a divalent arylene moiety, such as phenylene, methyl substituted phenylene, chlorophenylene, etc.; G' is O or S; and Y is a cycloalkyl ring, such as methylcyclohexyl, a substituted or unsubstituted aryl group or a heterocyclic such as 2-phenyl-4-oxazolyl; p is a number from 1 to 6. An illustrative Ar' group is shown in formula (II):



(II)

As is demonstrated in the Examples, the various C-substituted pentacycloazole compounds of this invention can be prepared by routine techniques. For example, C-substituted 2,3,5-triazoles can be prepared by reacting

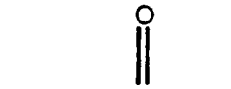
(1)  + hydrazine hydrate followed by cyclization with an isocyanate or

(2)  + 3-alkyl semicarbazide methane sulfonic acid salt or

(3) ArOH +  followed by hydrazine hydrate and then cyclized with an isocyanate or

(4) ArOH + N,N-dimethyl thiocarbamyl chloride

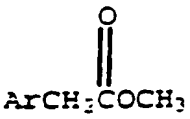
thermally rearranged, hydrolyzed, followed by  and then cyclization with an isocyanate, or

(5)  + hydrazine hydrate followed by cyclization with an isocyanate, etc.

A C-substituted 2,3-diazole can be prepared by reacting $ArCH_2CO_2R$ + Hydrazine hydrate followed by cyclization with CS_2.

A C-substituted 2,5-diazole can be prepared by reacting $ArCH_2CN + CH_3OH + HCl$ to form $ArC(=NH_2)OCH_3^+Cl^-$ followed by Na in CH_3OH to form an amidoxime and then treating with carbonyldiimidazole.

A C-substituted-1,3,4-oxathiazolin-5-one can be prepared by converting



to the amide followed by cyclization with chlorocarbonylsulfenyl chloride.

A C-substituted 1,2,4-thiadiazolin-5-one can be prepared by reacting $ArC(=NH_2)OCH_3^+Cl^-$ described above with sodium hydride and cyclizing with chlorocarbonylsulfenyl chloride.

A N-substituted azole can be prepared either by reaction route (1) or (2) below:

(1) Reacting ArCHO with semicarbazide hydrochloride followed by reduction with boron hydride and cyclizing with carbonyldiimidazole or;

(2) Reacting $ArCH_2NH_2$ with sodium cyanate and cyclizing with diethyl oxylate.

The compounds of this invention and salts thereof exhibit excellent blood-glucose and blood-lipid lowering actions in mammals (e.g., mouse, rat, dog, cat, monkey, horse, and human beings), and show a low degree of toxicity in terms of both acute and subacute toxicities. Therefore, the compounds and salts thereof are of value to human beings

for the treatment of hyperlipemia, diabetes and their complications.

The compounds of this invention are generally compounded with "pharmaceutically acceptable" carriers, diluents or excipients, which are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention. Preferably the pharmaceutical formulation is in unit dosage form. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. The compound can be administered by a variety of routes although oral is greatly preferred.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the compounds of the invention together with a pharmaceutically acceptable carrier or diluent therefor. In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a

carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration. For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl

cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter. Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both.

The active ingredient can also be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following Examples illustrate the preparation of compounds of the invention (unless otherwise indicated).

EXAMPLES

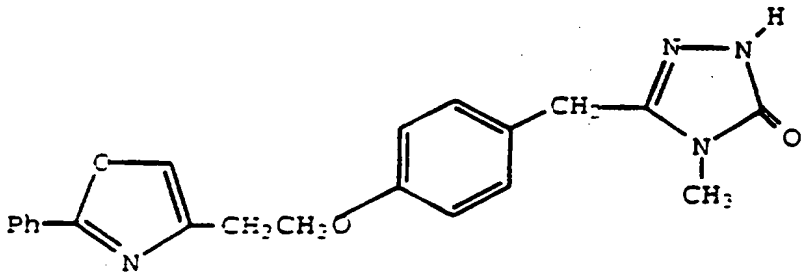
General Experimental Method:

Melting points are uncorrected. Thin Layer Chromatography was performed on silica plates. Reactions were conducted under an atmosphere of nitrogen. NMR spectra were obtained in $CDCl_3$ unless noted otherwise. Flash column chromatographies were performed over SiO_2.

2-(2-Phenyl-4-oxazolyl)ethanol was prepared as described in Example 12 Part A.

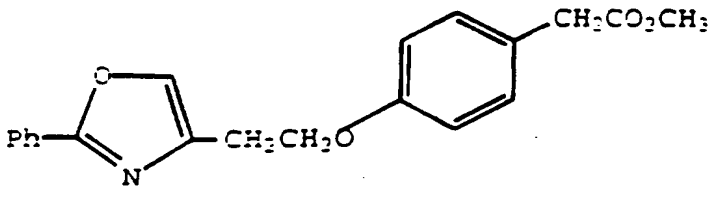
Example 1

Preparation of:
4-Methyl-5-[4-[(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]1,2,4-triazolin-3-one.



Part A

Preparation of:
Methyl 4-[2-(2-phenyl-4-oxazolyl)ethoxyl]phenyl acetate.



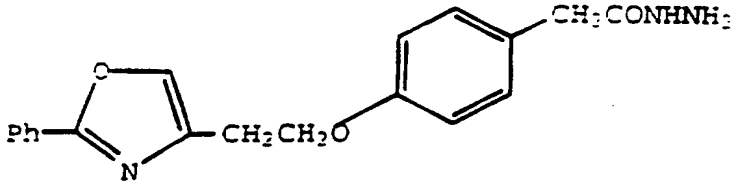
A stirred solution of 9.46 g 2-[2-phenyl-4-oxazolyl]ethanol, 8.34 g methyl (4-hydroxyphenyl)acetate, 13.10 g. triphenyl phosphine and 75 mL anhydrous THF (tetrahydrofuran) was treated dropwise with 7.9 mL diethyl azodicarboxylate over 15 minutes, allowing the temperature to rise spontaneously to 40-50°C. The reaction was stirred at ambient temperature for 48 hours, treated with 2 mL of 30% H_2O_2, and evaporated in vacuo. The residue was extracted with boiling Et_2O (ethyl ether), contacted with 75 mL of brine and dried over $MgSO_4$. After removal of the drying agent, the solvent was evaporated, the residue chromatographed, eluting with ethyl acetate-hexane. The product crystallized from ethylacetate-hexane to provide 14.8 g (88%), of a white solid mp 47-48°C.

Anal. Cal. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; Found: C, 71.43; H, 5.66; N, 4.07. IR 1734 cm^{-1}; NMR δ 3.15 (t, 2H), 3.6 (s, 3H), 3.7 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H, (7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H); MS:m/e 337.

Part B

Preparation of:

4-[2-[2-phenyl-4-oxazolyl)-ethoxy]phenyl acetyl hydrazine.



A stirred solution of 3.3 gm of methyl 4-[2-(2-phenyl-4-oxazolyl)ethoxy]phenyl acetate and 30 mL of MeOH was treated with 2.4 mL of 80% hydrazine hydrate, 0.5 gm of NaOMe and heated to reflux for 0.5 hour, during which time a

copious precipitate formed. The cooled mixture was filtered and the white solid washed with MeOH and dried to provide 2.86 gm (86%) of product mp 163-165°C.

Anal. Cal. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68 ; N, 12.46. Found: IR 1648 cm^{-1}. MS/m/e 333. NMR 1.6 delta (broad m, 2H), 3.1 (t, 2H), 3.5 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H, 7.8 (s, 1H).

Part C

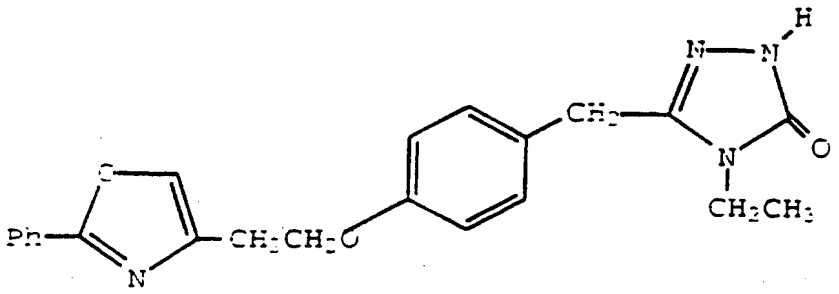
Preparation of:
4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]-1,2,4-triazolin-3-one.

The intermediate prepared in Example 1 Part B was suspended in 30 mL of THF (tetrahydrofuran), treated with 0.4 mL of methyl isocyanate and the stirred mixture heated to reflux for 2 hours. The mixture was cooled, diluted with Et_2O and filtered. The resulting white powder (0.97 gm, mp 191-194°C) was added to a solution prepared from 0.5 gm of Na metal and 25 mL of MeOH. The resulting solution was heated to reflux under an atmosphere of nitrogen for 5 hours, cooled and acidified with 1N HCl. The resulting precipitate was collected by filtration, washed with H_2O and dried. Recrystallization from THF-iPrOH provided 0.82 gm (86%) of product, mp 164-167°C.

Anal. Cal. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.75; H, 5.19; N, 14.63. Ir: 3302, 3072, 2933, 2854, 1691 cm^{-1}. Ms: m/e 376. NMR 1.7 (broad s, 1H, exchanges with D2O), 3.1 (s, 3H), 3.15 (t,2H), 3.85 (s,2H), 4.3 (t, 2H), 6.9 (d,2H), 7.2 (d,2H), 7.5 (m,4H), 7.8 (s,1H).

Example 2

Preparation of:
4-Ethyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]-1,2,4-triazolin-3-one.



Method 1

A suspension of 1.5 gm of the intermediate prepared as in Example 1 Part B was suspended in 30 mL of THF, treated with 0.4 mL of ethyl isocyanate and refluxed for 2 hours. The mixture was cooled, diluted with Et_2O and filtered. The white solid was collected, washed with Et_2O and added to a solution prepared from 1.4 gm of 85% KOH and 100 mL of MeOH. The resulting solution was heated to reflux for 24 hours, at which time TLC (thin layer chromatography) showed complete consumption of starting material. The cooled solution was acidified with 1N HCl and the resulting precipitate collected by filtration. Recrystallization from ETOAc (ethyl acetate) provided 0.89 gm (51%) of product as white needles mp 139-140°C.

Anal. Cal. for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 12.29. Found: C, 67.40; H, 5.78; N, 14.46. Ir: 1690cm^{-1}. MS: m/e 390. NMR: delta 1.05 (t, 3H), 3.1 (t, 2H), 3.5 (t, 2H), 3.95 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H).

Method 2

Part A. Preparation of:

3-Ethyl semicarbazide methanesulfonic acid salt.

A stirred solution of 25 gm tert-butyl carbazate in 200 mL $CHCl_3$ under nitrogen was treated dropwise over 0.5 hours with 16.5 mL ethyl isocyanate. The solution was stirred at room temperature 17 hours, treated with H_2O and the layers were separated. The aqueous layer was extracted with three 100 mL portions of $CHCl_3$ and the combined extracts were washed with brine, dried with Na_2SO_4, and filtered. Removal of the solvent in vacuo was followed by dissolution of the residue in 250 mL of dry THF. The resulting solution was treated dropwise with 22 mL of methane sulfonic acid over 0.5 hour. The resulting mixture was stirred at ambient temperature for 36 hours, during which time a precipitate formed. The solid was filtered and washed with THF and Et_2O to provide 24.2 gm (86%) of the salt mp 115-118°C.

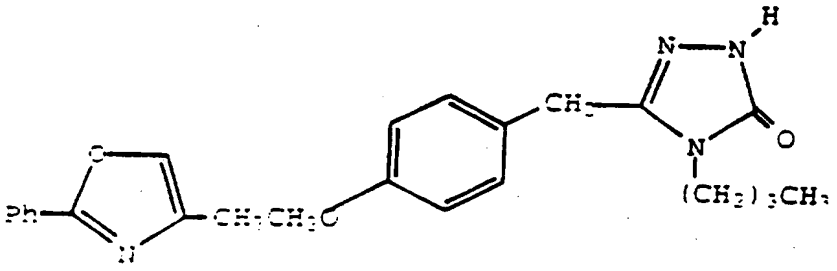
NMR: delta 1.04 (t, 3H), 2.37 (s, 3H), 3.10 (q, 2h), 7.08 (t, 1H), 8.59 (s, 1H), 9.76 (broad s, 2H) > MS: m/e 103 (= M - CH_3SO_3H).

Part B

To a solution prepared from 6.32 gm of Na metal and 200 mL of MeOH were added 2.95 gm of the salt from Method 2 Example 2 Part A and 5 gm of the intermediate prepared as in Example 1, Part A. The resulting mixture was refluxed for 100 hr, cooled and evaporated in vacuo. The residue was treated with 200 mL 2N HCl and extracted with three 100 mL portions of ETOAc. The combined extracts were washed with H_2O, brine, dried with Na_2SO_4, filtered, and the solvent removed in vacuo. Chromatography of the residue over silica produced 1.5 gm (26%) of product identical to the material prepared in Method 1.

Example 3

Preparation of:
4-n-Butyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]1,2,4-triazolin-3-one.

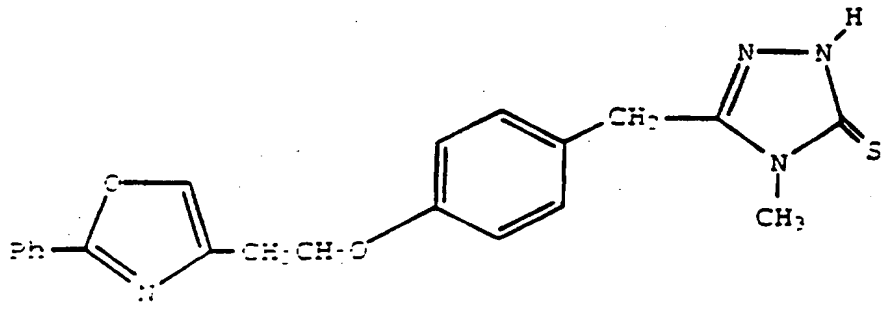


A suspension of 1.6 gm of the intermediate prepared as in Example 1 Part B in 40 mL of THF was treated with 0.8 mL of n-butyl isocyanate and heated to reflux for 2 hours. The cooled mixture was diluted with Et_2O and filtered. The white powder (1.9 gm, mp 172-175°C) was added to a solution prepared from 3.8 gm 85% KOH and 30 mL of MeOH and the resulting solution refluxed for a total of 48 hours. The cooled solution was acidified with 1N HCl and the soft white powder collected by filtration, washed with H_2O and dried. Recrystallization from i-PrOH-Hexane provided 1.01 gm (51%) of product mp 120-122°C.

Anal.: Cal. for $C_{24}H_{26}N_4O_3$. C, 68.88; H, 6.26; N, 13.39. Found: C, 68.63; H, 6.42; N, 12.82. MS: m/e 418. IR: 3401, 3063, 3063, 1702 cm^{-1}. NMR: 0.9 (t, 3H), 1.3 (m, m, 2H), 1.45 (m, 2H), 1.7 (broad s, 1H, exchanges with D_2O), 3.1 (t, 2H), 3.5 (t, 2H), 3.85 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H).

Example 4

Preparation of:
4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-thione.



Method 1

The intermediate prepared as in Example 1 Part 1 (2.48 gm) and 0.80 gm of 4-methyl thiosemicarbazide were added to a solution prepared from 0.72 gm of Na metal and 20 mL of MeOH. The resulting yellow solution was refluxed for 2 hours, cooled and acidified with 1N HCl. The resulting white precipitate was collected, washed with H_2O and dried. Recrystallization from THF-H_2O and from EtOAc provided 0.82 gm (28%) of 4-methyl-5-[4-((2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]-1,2,4-triazolin-3-thione, mp 189-190°C.

Anal.: Cal. for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.27. Found: C, 64.41; H, 5.22; N, 14.00. IR: 3099, 3042, 2939, 2878, 1574 cm^{-1}. MS: m/e 392. NMR: delta 3.1 (t, 2H), 3.35 (s, 3H), 4.0 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H).

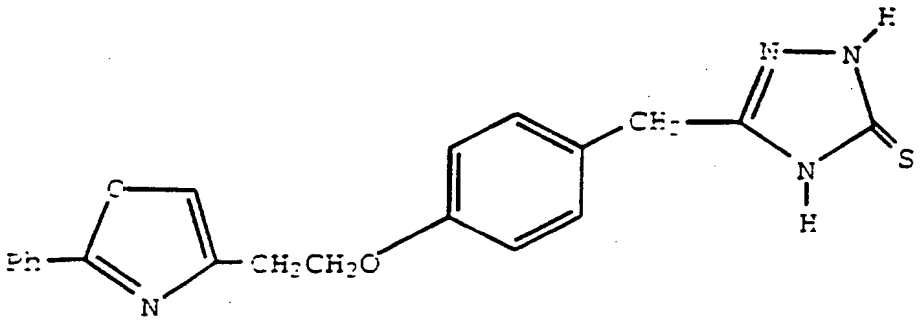
Method 2

A stirred suspension of 1.35 gm of the intermediate prepared as in Example 1 Part B in 30 mL of THF was treated

with 0.7 gm of methyl isothiocyanate and heated to reflux for 1 hour. The precipitate which formed on cooling was filtered and washed with ether. This solid (1.44 gm, mp 175-177°C) was added to a solution prepared from 0.8 gm of Na metal and 25 mL of MeOH and the resulting solution refluxed for 2 hours. The cooled solution was acidified with 1 N HCl and the resulting precipitate collected. Recrystallization from ETOAc provided 1.2 gm (76%) of 4-methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]-1,2,4-triazolin-3-thione. mp. 189-190°C, identical to that prepared in Example 4 Method 1.

Example 5

Preparation of:
1(3)H-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]1,2,4-triazolin-3-thione

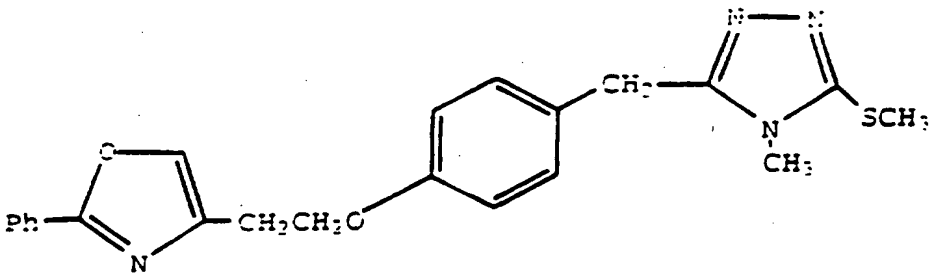


Thiosemicarbazide (1.90 gm) and 2.0 gm of the intermediate prepared as in Example 1 part A were added to a solution prepared from 0.6 gm of Na metal and 20 mL of 1-PrOH. The resulting mixture was heated to reflux for 3 hours and kept at room temperature overnight. The cooled mixture was acidified with 1N HCl and the solid filtered. Recrystallization from THF-MeOH provided 1.2 gm (53%) of product as a white solid mp 228-230°C.

Anal.: Cal. for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80. Found: C, 63.73; H, 4.85; N, 14.78. IR: 3096, 3029, 2928, 2877, 1609 cm^{-1}. MS: m/e 378. NMR: delta 3.1 (t, 2H), 4.0 (broad s, 2H exchanges with D_2O), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H).

Example 6

Preparation of:
3-Methylthio-4-methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazoline.



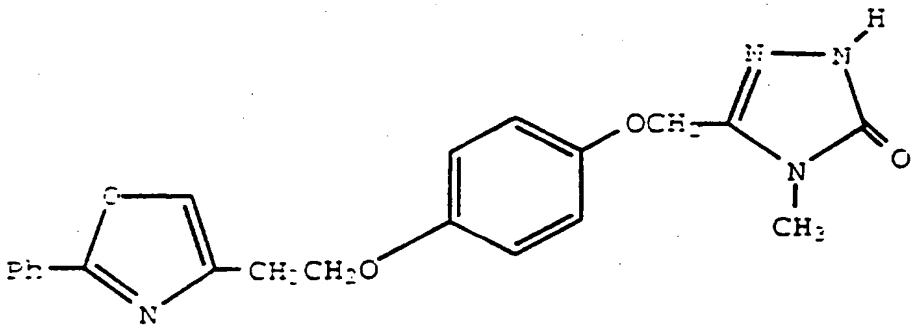
A stirred suspension of 2.42 gm of the intermediate prepared as in Example 1 Part B in 40 mL THF was treated with 2.1 gm of methyl isothiocyanate and refluxed for 3 hours. The reaction mixture was cooled and the solid filtered and washed with Et_2O. This solid was then added to a solution prepared from 1.5 gm of Na metal and 80 mL of MeOH and the resulting solution refluxed for 2 hours. The solution was allowed to cool with protection from atmospheric oxygen and treated with 5 mL of CH_3I. The resulting mixture was kept at room temperature overnight, treated with H_2O and extracted with three 125 mL portions of EtOAc. The combined extracts were washed with H_2O, brine, dried over $MgSO_4$ and evaporated to provide an oil which solidified on standing. Crystallization from EtOAc-hexane with the aid of

decolorizing carbon provided 1.62 gm (56%) of the product as glittering flakes mp 110-112°C.

Anal.: Cal. for $C_{22}H_{22}N_4O_2S$: C, 65.00 H, 5.45; N, 13.78. Found: C, 64.61; H, 5.44; N, 13.59. IR: 2914, 1550 cm^{-1}. MS: m/e 406. NMR: delta 2.7 (s, 3H), 3.1 (t, 2H), 3.3 (s, 3H), 4.15 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H).

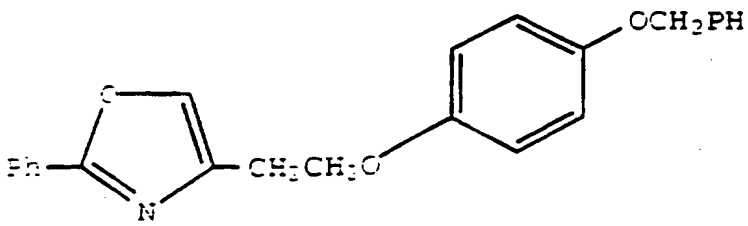
Example 7

Preparation of:
4-Methyl-5-[4-[(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl]2-oxaethyl]1,2,4-triazolin-3-one.



Part A.

Preparation of:
5-[(2-(2-Phenyl-4-oxazolyl)-ethoxyphenyl)] benzyl ether



A stirred solution of 38.7 gm 4-benzyloxyphenol, 37.4 gm triphenyl phosphine, 27.4 gm 3-(2-phenyl-4-

oxazolyl)ethanol and 200 mL THF was treated dropwise with 25 gm of diethyl azodicarboxylate over .25 hours, allowing the temperature to rise spontaneously to 50-60°C. The solution was kept at room temperature for 72 hours, treated with 2 mL of 30% H_2O_2 and the solvent removed in vacuo. The solid residual mass was dissolved in 350 mL of boiling EtOH and allowed to cool slowly. The white crystals which precipitated were filtered and washed with small portions of EtOH to provide 39.1 gm (75%) of needles mp 108-112°C.

Anal: Cal. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.35; H, 5.75; N, 3.50.MS: m/e 371.

Part B

Preparation of:

4-[2-(2-phenyl-4-oxazolyl)ethoxy] phenol.

A solution of the intermediate prepared in Example 7 Part A in 240 mL ETOH/280 mL THF was hydrogenated with 4 gm of 5% Pd/C at room temperature overnight with an initial hydrogen pressure of 60 psi (413.7 KPa). After removal of the catalyst by filtration, the solvents were removed in vacuo and the residue crystallized from i-PrOH to provide 24.7 gm (93%) mp 171-176°C.

Anal.: Cal. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.31; H, 5.40; N, 5.01. MS: m/e 281.

Part C

Preparation of:

Methyl O-4-[2-(2-phenyl-4-oxazolyl)ethoxy]phenylglycolic acid hydrazide.

A stirred solution of 5.40 gm of the intermediate from Example 7 Part B in 75 mL of methyl ethyl ketone was treated with 4 mL of methyl bromoacetate, 1.2 gm powdered KI, 11.1 gm powdered K_2CO_3 and heated to reflux for 4 hours. The

cooled mixture was diluted with H_2O, brine, dried over $MgSO_4$, filtered, and evaporated to provide an oil which solidified on trituration with hexane, mp 62-66°C. A solution of 2.36 gm of this solid in 25 mL MeOH was treated with 2 mL of 85% hydrazine hydrate, 0.2 gm of NaOMe and refluxed 1 hour, during which time a thick precipitate formed. The cooled mixture was filtered and the solid washed with MeOH and Et_2O to provide 2.20 gm (93%) of white powder mp 151-154°.

Anal.: Cal. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.71; H, 5.64; N, 11.70. MS: m/e 353.

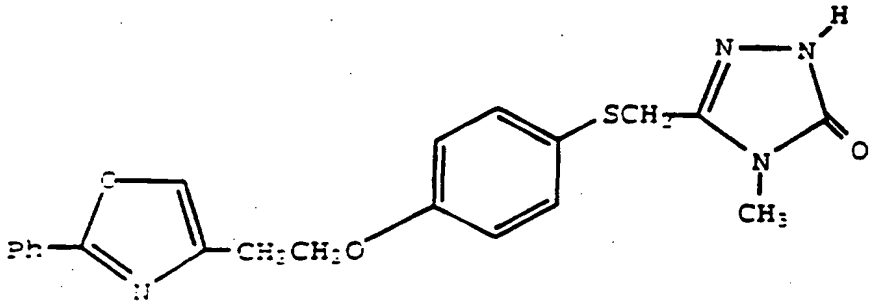
Part F

A stirred suspension of 1.46 gm of the intermediate from Example 7 Part C in 20 mL THF was treated with 1 mL methyl isocyanate and refluxed for 1 hour. The cooled mixture was diluted with Et_2O and filtered. The fine white powder was washed with Et_2O; mp 180-182°C. This solid was added to a solution prepared from 3.9 gm of 85% KOH/30 mL MeOH and the resulting solution refluxed 4 hours. An additional 1.8 gm of 85% KOH was added and the mixture refluxed an additional 3 hours, kept at room temperature overnight and acidified with 2N HCl. The solid obtained by filtration was washed with H_2O and dried to provide 0.94 gm (58%) of 4-methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)-phenyl)2-oxaethyl]1,2,4-triazolin-3-one mp 137-140°C.

Anal.: Cal. for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.27. Found: C, 64.48; H, 5.27; N, 14.04. MS: m/e 392. IR:1712, 1685 cm^{-1}. NMR: delta 3.1 (t, 2H), 3.35 (s, 3H), 4.3 (t, 2H), 4.9 (s, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H), 9.5 (broad s, 1H, exchanges with D2O).

Example 8

Preparation of:
4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)2-thiaethyl]1,2,4-triazolin-3-one.



Part B

Preparation of:
N,N-Dimethyl 4-[2-(2-phenyl-4-oxazolyl)ethoxy]-phenylthionocarbamate.

A stirred mixture of 15.5 gm of the intermediate prepared as in Example 7 Part B and 50 mL DMF was treated with 2.8 gm of 60% NaH/oil. Gas evolution occurred and was allowed to proceed at autogenous temperature for 0.25 hours. The resulting dark mixture was treated with 7.0 gm N,N-Dimethyl thiocarbamoyl chloride and stirred for 3 hours. The mixture was treated with ice and the thick curdy solid filtered. The solid was washed with H_2O, hexane and recrystallized from CH_2Cl_2-hexane (decolorizing carbon) to provide 13.3 gm (90%) of white flakes mp 111-113°C.

Anal.: Cal. for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.26; H, 5.50; N, 7.59. MS: m/e 368.

Part B

Preparation of:
N,N-Dimethyl 4-[2-(2-phenyl-4-oxazolyl)ethoxy]-phenylthiolcarbamate.

A stirred mixture of 4.15 gm of the intermediate from Example 8 Part A and 15 mL of tetraglyme was heated to reflux for a total of 17 hours and cooled. The dark solid mass was treated with hexane, heated to boiling, cooled and filtered. The tan flakes were washed thoroughly with hexane and dried to provide 3.68 gm (88%), mp 128-132°C.

Anal.: Cal. for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 64.97; H, 5.50; N, 7.52.

Part C

Preparation of:
Methyl S-4-[2-(2-phenyl-4-oxazolyl)ethoxy]phenylthioglycolic acid hydrazide.

A stirred mixture of 3.4 gm of the intermediate prepared in Example 8 Part B, 50 mL MeOH and 15 mL 2N NaOH was refluxed for 6 hours, cooled and acidified to pH4 with HOAc. The mixture was extracted with three 125 mL portions of EtOAc. The extracts were washed with H_2O, brine, dried over $MgSO_4$, filtered, and evaporated. The residual oil was dissolved in 30 mL of methyl ethyl ketone, the solution treated with 1.5 mL of methyl bromoacetate, 4.5 gm powdered K_2CO_3, 0.5 gm powdered KI and refluxed 2 hours. The cooled mixture was diluted with H_2O and extracted with three 50 mL portions of EtOAC. The extracts were washed with H_2O, brine, dried over $MgSO_4$, filtered, and evaporated to provide 4.5 gm of a semi-solid oil. A solution of 2.7 gm of this oil in 25 mL MeOH was treated with 2 mL 85% hydrazine hydrate, 0.1 gm NaOMe and refluxed 1 hour. The solution was kept at room temperature overnight, diluted with H_2O and the resulting precipitate filtered. The solid was washed with H_2O, dried

and recrystallized from i-PrOH-hexane to provide 2.93 gm (69% overall) of nearly white powder mp 118-121°C.

Anal.: Cal. for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.71; H, 5.20; N, 11.18. MS: m/e 369.

Part D

A stirred suspension of 1.2 gm of the intermediate from Example 8, Part C in 20 mL THF was treated with 1 mL of methyl isocyanate and the resulting solution stirred at ambient temperature for 2 hours. The solvent was removed by evaporation and the residue dissolved in 25 mL MeOH. The solution was treated with 2.8 gm of 85% KOH and heated to reflux for 7 hours. The mixture was kept at room temperature overnight, heated just to boiling to redissolve a small amount of solid and acidified with 5N HCl. The hot mixture was treated with ice, diluted with H_2O and the resulting solid filtered. The solid was washed with H_2O and recrystallized from i-PrOH-hexane to provide 0.47 gm (35%) of 4-methyl-5-[(2-(2-phenyl-4-oxazolyl)ethoxyphenyl)2-thiaethyl]1,2,4-triazolin-3-one mp 130-132°C.

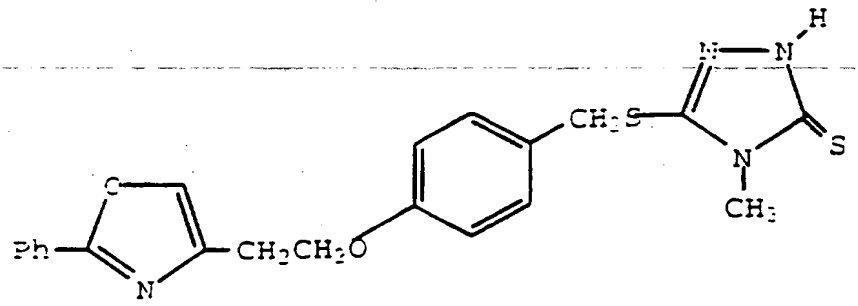
Anal.: Cal. for $C_{21}H_{20}N_4O_3S$: C, 61.75; H, 4.94; N, 13.72. Found: C, 61.99; H, 5.00; N, 13.42. MS: m/e 408. IR: 1725 1577 cm^{-1}. NMR: delta 3.1 (t, 2H), 3.3 (s, 3H), 3.8 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H), 8.7 (broad s, 1H, exchanges with D_2O).

Example 8A

This Example prepares a compound outside the scope of the invention (contrast to compound prepared in Example 8, supra.).

Preparation of:

4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-1-thiaethyl]1,2,4-triazolin-3-thione



Part A:

Preparation of:

Methyl 4-[2-(2-phenyl-4-oxazolyl)-ethoxy]benzoate.

A stirred solution of 14.2 g 2-(2-phenyl-4-oxazolyl)ethanol, 11.45 g methyl 4-hydroxybenzoate, 19.67 g triphenylphosphine and 150 mL THF was treated dropwise with diethyl azodicarboxylate (11.8 mL) over .5 hours allowing the temperature to rise spontaneously to 50-60°C. The reaction mixture was stirred at ambient temperature 24 hours, treated with 3 mL of 30% H_2O_2 and evaporated in vacuo. The residue was dissolved in 250 mL EtOAc, the solution was successively treated with 2N NaOH, H_2O, brine, dried over $MgSO_4$, and filtered. After removal of the solvent the residue was chromatographed over silica. The product was recrystallized from THF/hexane to provide 23.66 g (97%) of white flakes mp 100-102°C.

Anal.: Cal. for $C_{19}H_{17}NO_4$: C, 70.59; H, 5.30; N, 4.33. Found: C, 70.83; H, 5.33; N, 4.49.IR: 1707 cm^{-1}. (t, 2HO), 6.9 (d, 2h), 7.5 (m, 4H), 7.8 (s, 1h), 8.0 (m, 3H).

Part B:

Preparation of:
4-[2-(2-Phenyl-4-oxazolyl)-ethoxy]phenylmethanol.

A solution of 4.4 g of the intermediate prepared as in Example 8A, Part A in 50 mL THF was added dropwise to a stirred suspension of 2.7 g $LiAlH_4$ in 50 mL THF over 1 hour. The mixture was stirred an additional 1 hour and treated dropwise with 2 mL H_2O/8 mL THF, 4 mL %N NaOH, 8 mL H_2O, stirred and filtered. The white powder was washed with THF. The combined filtrate and washings were dried with K_2CO_3 and the solvent evaporated to provide an oil which solidified on scratching. Recrystallization from THF-hexane produced 4.02 g (98%) of fluffy powder mp 96-99°C.

Anal.: Cal. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.01; H, 5.82; N, 4.51. IR: 3526, 2881cm^{-1}. MS: m/e 295.

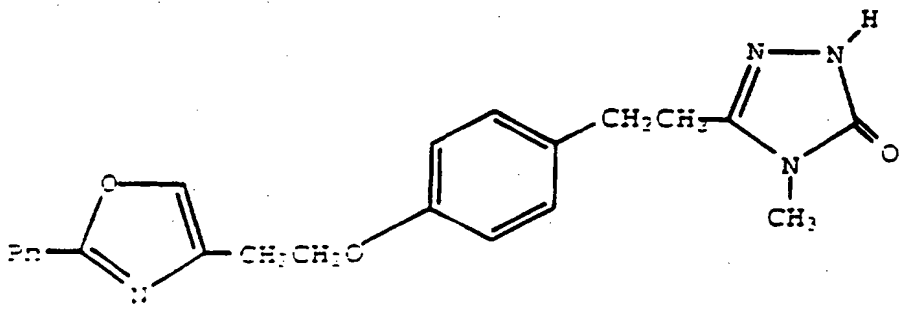
Part C

A stirred mixture of 1.40 g of the intermediate prepared as in Example 8A, Part B, 1.30 g 1-methyl-1,3,4-triazole-2,5-dithione and 30 mL i-PrOH was treated with 2.4 mL 48% HBr and heated to reflux for 3 hours. The cooled mixture was diluted with H_2O and filtered. The resulting white powder was washed with H_2O and filtered. The resulting white powder was washed with H_2O and recrystallized from THF/i-PrOH to provide 1.65 g (82%) of 4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-1-thiaethyl]1,2,4-triazolin-3-thione mp 173-175°C as fluffy white needles.

Anal.: Cal. for $C_{21}H_{20}N_4O_2S_2$: C, 59.41; H, 4.75; N, 13.20; S, 15.10. Found: C, 59.59; H, 4.80; N, 13.22; S, 14.81. MS: m/e 424. NMR: (DMSO-d_6): delta 3.1 (t, 2H), 3.35 (s, 3H), 4.3 (t, 2H), 4.35 (s, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 3H), 7.6 (s, 1H), 8.0 (m, 2H).

Example 9

Preparation of:
4-Methyl-5-[(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-2-ethyl]1,2,4-triazolin-3-one.



Part A

Preparation of:
4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenyl-3-propanoic acid hydrazide.

A stirred solution of 15.15 gm 2-(2-phenyl-4-oxazolyl)ethanol, 14.42 gm methyl 4-hydroxydihydrocinnamate, 20.98 gm triphenyl phosphine and 200 mL anhydrous THF was treated dropwise with 12.6 mL diethyl azodicarboxylate over 15 minutes, allowing the temperature to rise spontaneously to 50-60°C. The solution was stirred at ambient temperature for 48 hours, treated with 2 mL 30% H_2O_2 and evaporated in vacuo. The residue was dissolved in 250 mL of EtOAc and the solution washed successively with 2N NaOH, H_2O, brine and dried over $MgSO_4$. After removal of solvent the residue was chromatographed over silica to provide 21.93 gm (78%) of ester mp 47-48°C. A solution of 3.51 gm of ester in 25 mL of MeOH was treated with 4 mL 85% hydrazine hydrate, 0.1 gm NaOMe and refluxed 2 hours. The cooled mixture was diluted with H_2O and the solid filtered. The solid was washed with

H_2O and dried to provide 3.4 gm (97%) of product mp 144-145°C.

Anal.: Cal. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.40; H, 6.06; N, 11.84. MS: m/e 351.

Part B

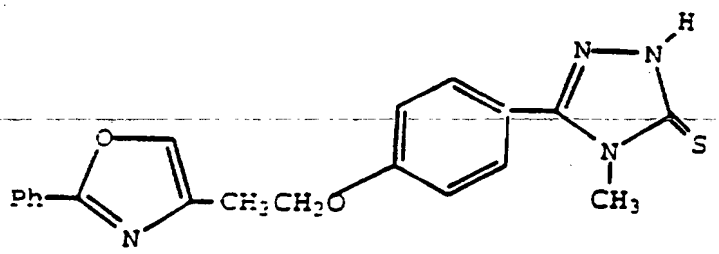
A sample of 4.04 gm of the hydrazide prepared in Example 9 Part A was suspended in 40 mL THF and treated with 0.6 mL of methyl isocyanate. The mixture was refluxed 1 hour, cooled, diluted with Et_2O and filtered. The white solid (3.5 gm, mp 166-168°C was added to a solution prepared from 1.6 gm of Na metal and 25 mL of MeOH and the resulting solution refluxed for 6 hours. The cooled solution was acidified with 2N HCl and the resulting white solid filtered, washed with H_2O and dried. Recrystallization from i-PrOH provided 2.7 gm (50%) of 4-methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)-phenyl)-2-ethyl]1,2,4-triazolin-3-one mp 127-129°C.

Anal.: Cal. for $C_{22}H_{24}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.56; H, 5.69; N, 14.57. MS: m/e 390. NMR: delta 2.75 (t, 2H), 2.95 (t, 2H), 3.05 (s, 3H), 3.1 (t, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H), 9.3 (broad s, 1H, exchanges with D_2O).

Example 9A

This Example prepares a compound outside the scope of the invention (contrast to compound prepared in Example 9, supra.).

Preparation of:
4-Methyl-5-[4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl]1,3,4-triazolin-3-thione.



Part A:

Preparation of:

4-[2-(2-Phenyl-4-oxazolyl)ethoxy]benzoylhydrazine.

A stirred solution of 3.23 g of the intermediate prepared as in Example 8A, Part A in 40 mL MeOH was treated with 5 mL of 80% hydrazine hydrate, 0.1 g NaOMe and heated to reflux for 3 hours. The cooled mixture was diluted with H_2O and filtered. The white solid was washed with H_2O and dried to provide 3.00 g (97%) of hydrazide mp 157-159°C.

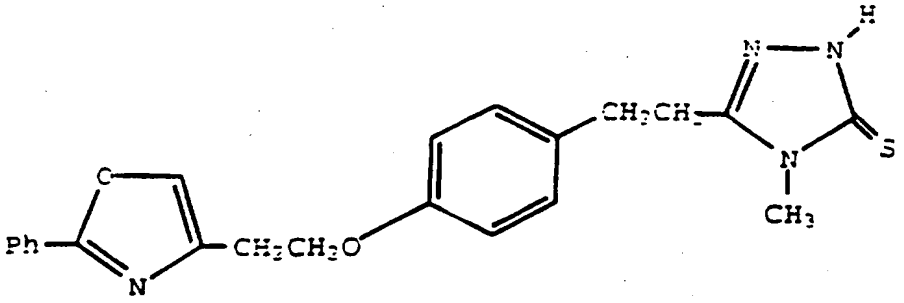
Part B

A stirred mixture of 1.89 g of the intermediate prepared as in Example 9A Part A in 40 mL THF was treated with 1.06 g methyl isothiocyanate and heated to reflux for 1 hour. The resulting solution was kept at room temperature 12 hours and evaporated in vacuo. The residue was boiled with EtOH, cooled and filtered. The white solid was washed with Et_2O and added to a solution prepared from 0.64 g Na metal/25 mL MeOH. The resulting mixture was heated to reflux 3 hours, cooled and treated with 100 mL 2N HCl. The resulting precipitate was filtered, washed with H_2O and recrystallized from THF/i-PrOH to provide 2.12 g (91%) of 4-Methyl-5-[4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl]1,3,4-triazolin-3-thione mp 188-190°.

Anal.: Cal. for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.80. Found: C, 63.45; H, 4.88; N, 14.79. IR: 3120, 1610 cm^{-1}. MS: m/e 378. NMR: delta 3.1 (t, 2H), 3.7 (s, 3H, 4.4 (t, 2H, 7.1 (d, 2H), 7.5 (m, 3H), 7.6 (d, 2H), 7.65 (s, 1H), 8.0 (m, 2H).

Example 10

Preparation of:
4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-2-ethyl]1,2,4-triazolin-3-thione.

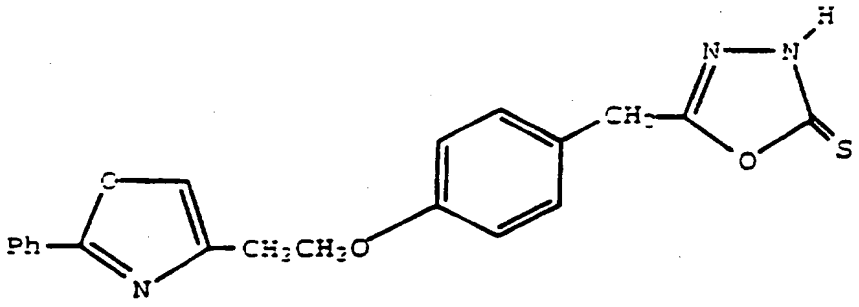


A suspension of 1.75 gm of the intermediate prepared as in Example 9 Part A and 25 mL THF was treated with 0.8 gm methyl isothiocyanate and refluxed 1 hour. The resulting solution was kept at room temperature 12 hours, and diluted with hexane. The resulting solid was filtered, washed with hexane and recrystallized from EtOH to give 1.34 gm of white powder mp 142-144°C. This powder was added to a solution prepared from 0.7 gm Na metal and 20 mL MeOH and refluxed for 2 hours. The cooled solution was acidified with 2N HCl, diluted with H_2O and stirred at room temperature overnight. The solid was filtered, washed with H_2O, dried and recrystallized from THF-i-PrOH to provide 1.14 gm (56%) of 4-methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-2-ethyl] 1,2,4-triazolin-3-thione mp 152-154°C.

Anal.: Cal. for $C_{22}H_{22}N_4O_2S$: C, 65.00; H, 5.45; N, 13.78. Found: C, 64.71; H, 5.44; N, 13.65. MS: m/e 406. NMR: delta 2.75 (t, 2H), 2.9 (s, 2H), 3.0 (s, 2H), 3.1 (t, 2H), 3.4 (s, 3H), 4.9 (s, 1H, exchanges with D_2O), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H).

Example 11

Preparation of:
5-[4-((2-(2-phenyl-4-oxazolyl)-ethoxy)phenyl)methyl]1,2,4-oxadiazolin-3-thione.



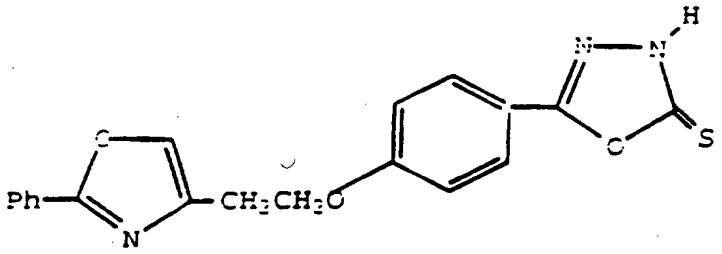
A stirred suspension of 3.37 gm of the intermediate prepared as in Example 1 Part B, 0.84 gm 85% KOH and 30 mL EtOH was treated with 0.6 mL CS_2 and heated to reflux 8 hours. The mixture was kept at room temperature overnight, the solvent evaporated in vacuo and the residue treated with 1N HCl. The white solid was filtered, washed with H_2O and dried. Chromatography over silica followed by several recrystallizations from THF-hexane provided 1.07 gm (28% of product mp 194-197°C.

Anal.: Cal. for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07. Found: C, 63.60; H, 4.82; N, 1080. MS: m/e 379. IR: 1625 cm^{-1}. NMR: delta 3.1 (t, 2H), 4.05 (s, 2H), 4.3 (t, 2H), 6.9 (d, 2H), 7.2 (d, 2H), 7.5 (m, 4H), 7.8 (s, 1H).

Example 11A

This Example prepares a compound outside the scope of the invention (contrast to compound prepared in Example 11, supra.).

Preparation of:
5-[4-(2-(2-Phenyl-4-oxazolyl)-ethoxy]phenyl-1,3,4-oxadiazole-2-thione.



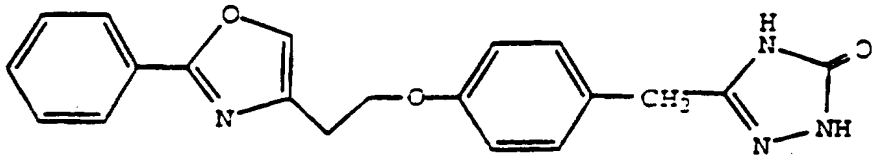
A stirred mixture of 4.05 g of the intermediate prepared as in Example 9A, Part A and 75 mL MeOH was treated with 1 mL carbon disulfide, 4.0 g of KOH and heated to reflux for 12 hours. An additional 1 mL carbon disulfide was added and refluxing continued for an additional 24 hours. The mixture was stirred at ambient temperature for 36 hours, neutralized with HOAc and concentrated. The residue was chromatographed to provide 1.73 g (38% of white powder mp 229-231°C).

Anal.: Cal. for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.12; N, 11.50. Found: C, 62.66; H, 4.41; N, 11.23. IR: 2878, 1614 cm^{-1}. MS: m/e 365. NMR: delta 3.1 (t, 2H), 3.4 (broad s, 1H, exchanges with D_2O), 4.4 (t, 2HO, 7.15 (d, 2H), 7.5 (m, 3H), 7.8 (d, 2H), 8.0 (m, 2H), 8.1 (s, 1H).

Example 12

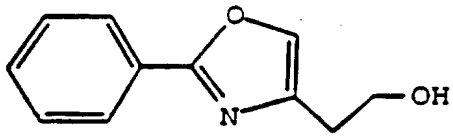
Preparation of:

5-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]-1,2,4-triazolin-3-one.



Part A

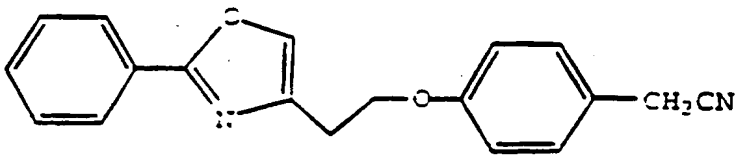
Preparation of:



To an ice-cooled suspension of 5.87 g (0.155 mol) of $LiAlH_4$ in 700 mL of Et_2O was added a solution of 35.53 g (0.154 mol) of ethyl 2-phenyl-4-oxazoleacetate in 300 mL of Et_2O over a 1.5 hour period. The temperature of the reaction during the addition was kept below 15°C. After stirring for 2 hours at 25°C the reaction was decomposed by the addition of 15 mL of EtOAc and 33.5 mL of H_2O. The mixture was filtered through anhydrous Na_2SO_4 and concentrated in vacuo to leave 28.1 g of oil. Distillation of the crude oil gave 2-(2-phenyl-4-oxazolyl)ethanol (23.52 g, 81%, bp 120-122°C/.05-.06 mm) as an oil which solidified on standing. Elemental analysis for $C_{11}H_{11}NO_2$. Calcd.: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.78; H, 5.90; N, 7.49.

Part B

Preparation of:

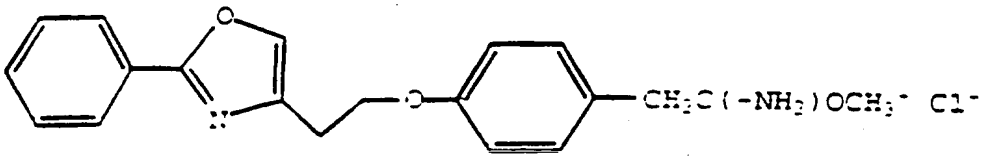


To a solution of 5.15 g (.0272 mol) of product of Example 12 Part A, 4.83 g (.0363 mol) p-hydroxybenzyl nitrile and 8.20 g (.0313 mol) triphenylphosphine in 85 mL of freshly distilled THF at 0°C was added 4.70 mL diethyl azodicarboxylate over a 15 minute period. The reaction mixture was stirred at 25°C for 16 hours and then treated with 1.5 mL of 30% H_2O_2 followed by 100 mL of Et_2O. The organic layer was washed successively with 1N NaOH and H_2O. After drying over anhydrous Na_2SO_4 and filtering the solvent was removed. Addition of Et_2O precipitated triphenylphosphine oxide which was removed by filtration. The residue after removal of the solvent was chromatographed on silica. Elution with CH_2Cl_2 gave 4-[2-(2-phenyloxazolyl)ethoxy]phenyl-acetonitrile (5.46 g, 66%, mp 81-83°C).

Elemental analysis for $C_{19}H_{16}N_2O_2$. Calcd.: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.08; H, 5.38; N, 8.98.

Part C

Preparation of:



Method 1:

A solution of 1.0 g (3.29 mmol) of product of Example 12 Part B and 0.146 mL of anhydrous MeOH in 10 mL of CH_2Cl_2 at 0°C was saturated with gaseous HCl and kept for 20 hours in the cold. The reaction mixture was evaporated to dryness in vacuo to leave 1.2 g of 4-[2-(2-phenyl-4-oxazolyl)ethoxy]benzeneethanimidic acid methyl ester hydrochloride as a white solid, mp 182-184°C.

NMR ($CDCl_3$): delta 3.327 (t, 2H), 4.000 (s, 2H), 4.257 (s, 3H), 4.387 (t, 2H), 6.911 (d, 2H), 7.359 (d, 2H), 7.543-7.649 (m, 3H), 7.759 (s, 1H), 8.329 (d, 2H), 11.790 (br.s, 1H), 12.783 (br.s., 1H).

Method 2:

A stirred mixture of 7.8 g of nitrile from Example 12 Part B and 80 mL of MeOH was cooled to 0°C and gaseous HCl was introduced for 1 hour until dissolution occurred. Anhydrous Et_2O (700 mL) was added and the resultant oil was washed with Et_2O and solidified on standing leaving crude 4-[2-(2-phenyl-4-oxazolyl)ethoxy]-benzeneethanimidic acid methyl ester hydrochloride.

Part C

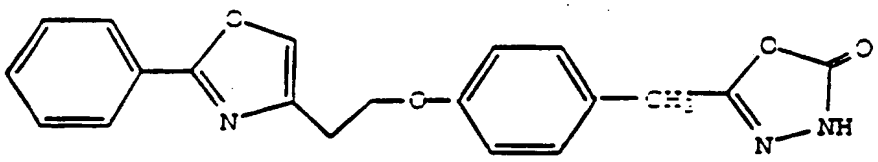
Preparation of Example 12:

A mixture of 5.8 g of iminoether product of Example 12 Part C Method 1, 1.75 g of semicarbazide HCl, 100 mL of Py (pyridine) and 100 mL of DMF (dimethyl formamide) was refluxed for 5 hours. After cooling, H_2O was added and the mixture was evaporated in vacuo and crystallized from a mixture of MeOH-H_2O and washed with CH_2Cl_2 leaving 1.21 g of 5-[(4-[2-(2-phenyl-4-oxazolyl)ethoxy]phenyl)methyl]-1,2,4-triazolin-3-one as a white solid (20%, mp 222-229°C).

Elemental analysis for $C_{20}H_{18}N_4O_3$, Calcd.: C, 66.29; H, 5.01; N, 15.46. Found: C, 66.14; H, 5.11; N, 15.41. FD-MS m/e 362; NMR (DMSO-d6): delta 2.944 (t, 2H), 3.585 (s, 2H), 4.195 (t, 2H), 6.870 (d, 2H), 7.113 (d, 2H), 7.464-7.482 (m, 3H), 7.898 - 7.928 (m, 2H), 7.983 (s, 1H), 11.104 (s, 1H), 11.198 (s, 1H).

Example 13

Preparation of:
5-[[4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenyl]methyl]-1,3,4-oxadiazolin-2-one.



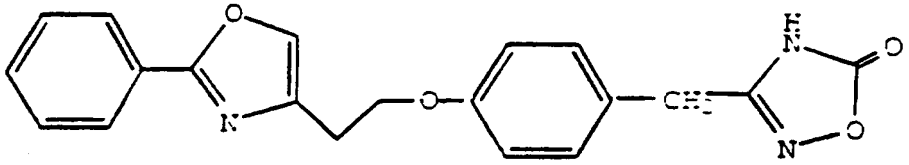
A solution of 1.4 mL of phenyl chloroformate in 20 mL of CH_2Cl_2 was added to a stirred mixture of 3.45 g of hydrazide from Example 1 Part B, 1.5 mL of Py and 800 ml of CH_2Cl_2 at 15°C. After stirring for two days at 25°C, 630 mL of solvent was removed and the mixture was stirred for another five days. Methylene chloride was added to bring the total volume to 500 mL and the reaction was washed successively with aqueous $NaHCO_3$, aqueous 5% citric acid, H_2O and dried over anhydrous Na_2SO_4. Evaporation of the solvent after filtration left 4.9 g of residue which was chromatographed on 120 g of silica. Elution with 1-2% MeOH in CH_2Cl_2 gave 1.9 g of a mixture of intermediate phenoxycarbonyl hydrazide and product 1,3,4-oxadiazol-2-one. Further elution with 3% MeOH in CH_2Cl_2 provided 1.3 g of recovered starting hydrazide.

The 1.9 g of the above mixture was dissolved in 175 mL of EtOH and treated with 30 ml of 1N NaOH for 2.5 hours at 25°C. After acidification with aqueous HCl, the solvent was removed and the residue was dissolved in $CHCl_3$, washed with H_2O and brine and dried over anhydrous Na_2SO_4. Removal of the solvent left 2.0 g of white solid which was recrystallized from 50 mL of MeOH to give 1.3 g of 5-[(4-(2-(2-phenyl-4-oxazolyl)-ethoxy)phenyl)methyl]1,3,4-oxadiazolin-2-one (56%, mp 142-144°C).

Elemental analysis for $C_{20}H_{17}N_3O_4$. Calcd.: C, 66.11, H, 4.72, N, 11.56. Found: C, 65.84, H, 4.90, N, 11.34. FD-MS: m/e 363; NMR (DMSO-d6): delta (t, 2H), 3.799 (s, 2H), 4.209 (t, 2H), 6.903 (d, 2H), 7.155 (d, 2H), 7.463-7.483 (m, 3H), 7.905 - 7.931 (m, 2H), 7.988 (s, 1H), 12.072 (br.s, 1H).

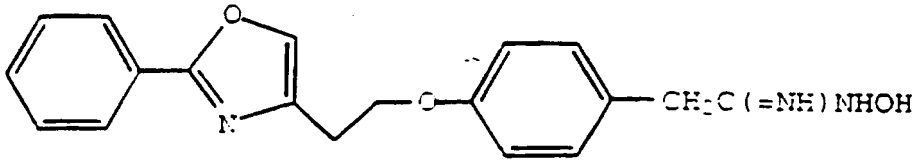
Example 14

Preparation of:
3-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-oxadiazolin-5-one.



Part A

Preparation of:



To a cooled (0°C) solution of 0.88 g of Na in 80 mL of anhydrous MeOH was added 2.67 g of NH_2OH HCl followed by a solution of the iminoether of Example 12 Part C Method 2 in 100 mL of anhydrous MeOH. The reaction mixture was allowed to warm to 25°C and was stirred for 18 hours. The residue, after removal of solvent, was partitioned between 200 mL of H_2O and 700 mL of EtOAc. The solid was removed by filtration and washed with H_2O and EtOAc. The combined organic phases were washed with H_2O and combined with the solid. After removal of the solvent, the residue was recrystallized from MeOH. The filtrate was diluted with Et_2O and the resulting solid was filtered to give 4.14 g of crude N-hydroxy-4-[2-(2-phenyl-4-oxazolyl)ethoxy]benzeneethanimidamide. FD-MS: m/e 337.

Part B

Preparation of Example 14:

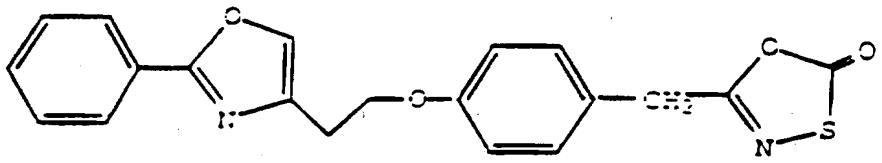
A mixture of 4.06 g of the amidoxime from Example 14 Part A, 150 mL of THF and 1.98 g of carbonyldiimidazole was heated at reflux for 7 hours, cooled to 25°C, and stirred another 16 hours. The solvent was removed in vacuo. The residue was dissolved in 600 mL of EtOAc, washed with H_2O and dried over anhydrous Na_2SO_4. The residue, obtained after filtration and evaporation of the solvent, was recrystallized from EtOH to give 3.11 g of 3-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]1,2,4-oxadiazolin-5-one (71%, mp 154.5-157.5°C).

Elemental analysis for $C_{20}H_{17}N_3O_4$, Calcd.: C, 66.11; H, 4.72; N, 11.56. Found: C, 66.32; H, 4.77; N, 11.34. NMR (DMSO-d6): delta (t, 2H), 3.747 (s, 2H), 4.210 (t, 2H), 6.906 (d, 2H), 7.167 (d, 2H), 7.464-7.483 (m, 3H), 7.905-7.929 (m, 2H), 7.988 (s, 1H), 12.232 (br.s, 1H).

Example 15

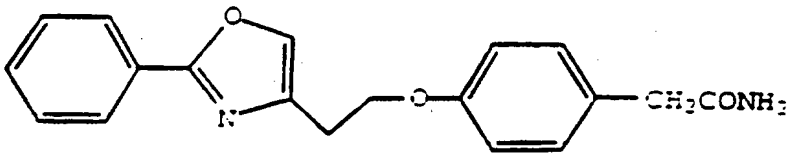
Preparation of:

5-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,3,4-oxathiazolin-2-one



Part A

Preparation of:



A solution of 0.5 g of methyl ester of Example 1 Part A, 50 mL of MeOH, 0.2 g of NH_4Cl and 40 mL of NH_4OH was stirred at 25°C for 48 hours with brief, intermittent warming at 50°C. The MeOH was partially removed, and the reaction mixture was diluted with H_2O. The solid precipitate was filtered, washed with H_2O and dried to give 4-(2-(2-phenyl-4-oxazolyl)ethoxy)-phenylacetamide (0.39 g, 82%, mp 180-183.5°C).

Elemental analysis for $C_{19}H_{18}N_2O_3$, Calcd.: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.54; H, 5.72; N, 8.50. FD-MS: m/e 322; NMR (DMSO-d6): delta 3.968 (t, 2H), 3.250 (s, 2H), 4.214 (t, 2H), 6.788 (br.s, 1H), 6.865 (d, 2H), 7.350 (d, 2H), 7.354 (br.s, 1H), 7.493-7.504 (m, 3H), 7.928-7.954 (m, 2H), 8.008 (s, 1H).

Part B

Preparation of Example 15:

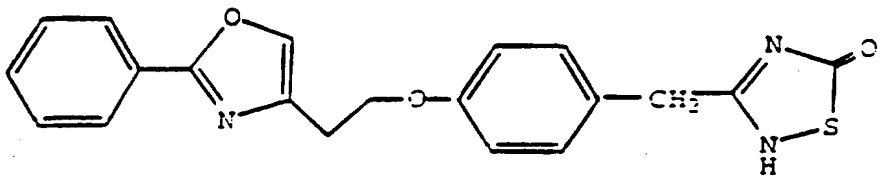
To a stirred mixture of 3.6 g of amide of Example 15 Part A and 200 mL of toluene at 82°C was added dropwise 1.05 mL of chlorocarbonylsulfenyl chloride. The reaction was heated for 7 hours at 82°C and stirred an additional 18 hours at 25°C. The volatiles were removed in vacuo, and the residue was partitioned between $CHCl_3$ and H_2O. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were evaporated and chromatographed on 87 g of silica. Elution with 0.5% MeOH in CH_2Cl_2 gave 1.7 g solid which was recrystallized from a mixture of acetone and Et_2O to give 1.4 g of 5-[(4-(2-(2-phenyl-4-oxazolyl)-ethoxy)phenyl)methyl]1,3,4-oxathiazolin-2-one (29%, mp 103-105°C).

Elemental analysis for $C_{20}H_{16}N_2O_4S$. Calcd.: C, 63.15; H, 4.24; N, 7.36. Found: C, 63.01; H, 4.28; N, 7.31. FD-MS: m/e 380; NMR ($CDCl_3$): delta 2.962 (t, 2H), 3.938 (s, 2H), 4.223 (t, 2H), 6.918 (d, 2H), 7.203 (d, 2H), 7.459-7.503 (m, 3H), 7.909-7.938 (m, 2H), 7.998 (s, 1H).

Example 16

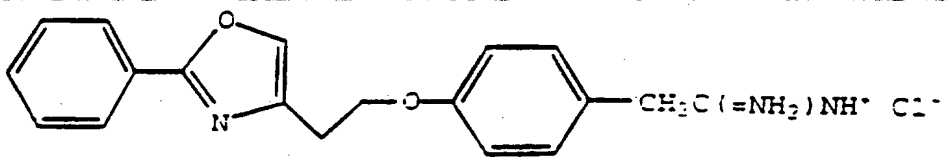
Preparation of:

3-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-thiadiazolin-5-one.



Part A

Preparation of:



To a mixture of 4-(2-(2-phenyl-4-oxazolyl)ethoxy)benzene-ethanimidic acid methyl ester hydrochloride of Example 12 Part C, obtained from 20.0 g of nitrile Example 12 Part B, 3.6 g of NH_4Cl and 200 mL of anhydrous MeOH was added 100 mL of anhydrous NH_4OH saturated with NH_3. The reaction mixture was stoppered and stirred at 25°C for 16 hours. The volatiles were removed in vacuo and the solid was treated with H_2O and with MeCN and dried to leave 21.4 g of 4-(2-(2-phenyl-4-oxazolyl)-ethoxy)benzeneethanimidamide hydrochloride, mp 187-194°C. A 4.94 g portion of solid was dissolved in 50 mL of refluxing MeOH, filtered, and diluted with 80 mL of MeCN. Most of the MeOH was evaporated and the solution was cooled and allowed to crystallize. Filtration gave 4.45 g of 4-(2-(2-phenyl-4-oxazolyl)ethoxy)benzeneethanimidamide hydrochloride as a white solid after washing with Et_2O, mp 191-193°C.

Elemental analysis for $C_{19}H_{19}N_3O_2$. Calcd.: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.49; H, 5.72; N, 11.71.

Part B

Preparation of Example 16:

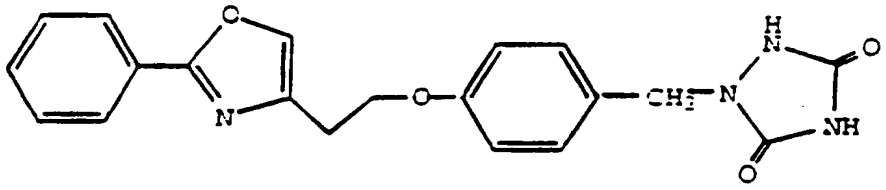
To a stirred suspension of 1.9 g of 60% NaH in mineral oil and 440 mL of freshly distilled THF was added 17.0 g of solid crude imidamide hydrochloride of Example 16

Part A. The mixture was stirred for 2.5 hours at 25°C and 25.0 g of diisopropylethyl amine was added followed by 3.70 mL of chlorocarbonylsulfenyl chloride. After stirring for 18 hours, the reaction mixture was poured into H_2O and extracted with EtOAc. The EtOAc layer was washed with H_2O, brine and dried over anhydrous Na_2SO_4. After filtrtion and evaporation of the solvent, the dark oil was chromatographed on 220 g of silica. Elution with 1% MeOH in CH_2Cl_2 afforded 8.2 g of solid which was recrystallized twice from a mixture of CH_2Cl_2 and hexanes to give 7.40 g of 3-[(4-(2-(2-phenyl-4-oxazolyl ethoxy)phenyl -methyl]1,2,4-thiadiazolin-5-one (41%, mp 160-163°C).

Elemental analysis for $C_{20}H_{17}N_3O_3S$. Calcd.: C, 63.31, H, 4.52, N, 11.07. Found: C, 63.10; H, 4.61; N, 11.07. FD-MS: m/e 379; NMR (DMSO-d6): delta 2.991 (t, 2H), 3.746 (s, 2H), 4.223 (t, 2H), 6.908 (d, 2H), 7.172 (d, 2H), 7.924-7.967 (m, 3H), 8.002 (s, 1H), 12.823 (br.s., 1H).

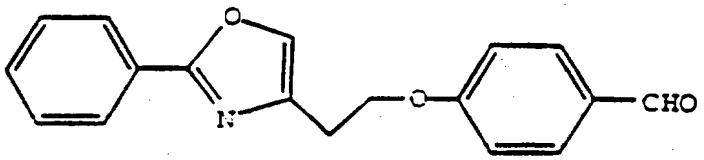
Example 17

Preparation of:
1-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolidin-3,5-dione.



Part A

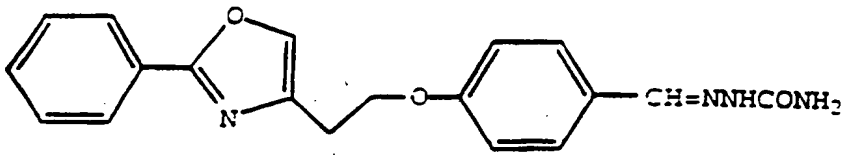
Preparation of:



To a solution of 72.7 g of alcohol product of Example 9A, Part A, 47.9 of 4-hydroxybenzaldehyde, 104 g triphenylphosphine and 450 mL of anhydrous THF at -5°C was added 75 g of diethyl azodicarboxylate over a 20 minute period. The temperature was maintained at 0°C. The cooling bath was removed and the reaction mixture was stirred for 20 hours at 25°C. After the addition of 5 mL of 30% H_2O_2 the reaction mixture was diluted with 1.2 L of Et_2O, washed with 1 N NaOH and H_2O and dried over Na_2SO_4. The solvent was removed and the residue was dissolved in 1 L of Et_2O and cooled to 0°C. The solid which precipitated (Ph_3PO) was removed by filtration and the filtrate was concentrated to 600 mL and cooled to 0°C. The precipitate was filtered and recrystallized twice from acetone/H_2O to give 4-[2-(2-phenyl-4-oxazolyl)ethoxy]-benzaldehyde (28.9 g, mp 92-97°C). An additional 32.6 of product (total yield 61.5 g, 54%) was obtained from filtrates.

Elemental analysis for $C_{18}H_{15}NO_3$, Calcd.: C, 73.71; H, 5.15; N, 4.77. Found: C, 73.84; H, 5.34; N, 5.02. FD-MS: m/e 293. NMR (DMSO-d6): delta 3.006 (t, 2H), 4.354 (t, 2H), 7.120 (d, 2H), 7.453-7.485 (m,3H), 7.817 (d, 2H), 7.902-7.932 (m, 2H), 8.018 (s, 1H), 9.820 (s, 1H).

Part B:

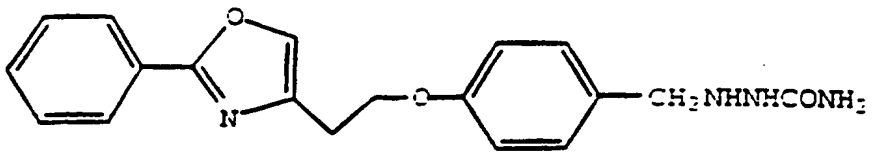


A mixture of 20.0 g of aldehyde from Example 17 Part A, 8.29 g of semicarbazide hydrochloride, 8.14 g of NaOAc and 150 mL of H_2O was heated for 0.75 hours at 100°C with occasional swirling. The heterogenous mixture was diluted with 150 mL of MeOH and allowed to stand at 25°C for 64 hours. The solid was filtered and washed with H_2O, refluxed with 500 mL of MeOH and filtered hot leaving 21.3 g of 4-(2-(2-phenyl-4-oxazolyl)ethoxy)benzaldehyde semicarbazone (89%, m.p. 221-226°C).

Elemental analysis for $C_{19}H_{18}N_4O_3$. Calcd.: C, 65.13; H, 5.18; N, 15.99. Found: C, 64.91; H, 5.20; N, 15.73.

Part C

Preparation of:



A mixture of 26.1 g of semicarbazone of Example 17 Part B in 500 mL of THF was treated with 298 mL of a 1N BH_3 in THF solution. After stirring for 14 hours at 25°C the solution was slowly poured into 600 mL of MeOH. The reaction mixture was evaporated in vacuo to dryness. The solid was

treated twice with 600 mL of MeOH by refluxing and evaporating the volatiles. The residue was then diluted with 400 mL of MeOH, cooled to 0°C and filtered leaving 22.4 g N1-[4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl]methylsemicarbazide (85%, mp 192-196°C).

Elemental analysis for $C_{19}H_{20}N_4O_3$. Calcd.: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.58; H, 5.67; N, 15.64. NMR (DMSO-d6): delta 2.951 (t, 2H), 3.655 (d, 2H), 4.203 (t, 2H), 4.823 (br.s, 1H), 5.732 (br.s, 2H), 6.856 (d, 2H), 7.207 (d, 2H), 7.466-7.485 (m, 3H), 7.902-7.932 (m, 2H), 7.993 (s, 1H).

Part D

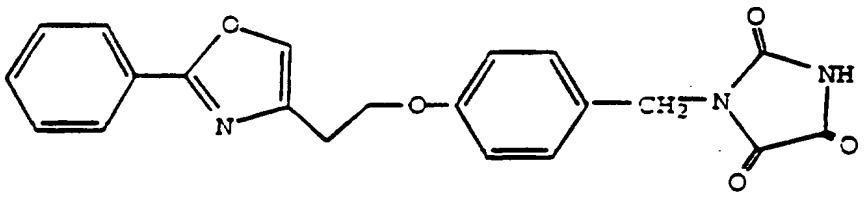
Preparation of Example 17:

A mixture of 11.9 g of semicarbazide from Example 17 Part C, 8.10 g of carbonyldiimidazole, 0.5 mL of triethylamine and 400 mL of anhydrous DMF was stirred at 25°C for 4 days, diluted with 1 L of H_2O and filtered. The filtrate was evaporated. The residue was treated with 100 mL of MeOH and the solid was filtered and dried to give 3.43 g of 1-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolidin-3,5-dione (27%, mp 223.5-230°C).

Elemental analysis for $C_{20}H_{18}N_4$. Calcd.: C, 63.49; H, 4.80; N, 14.81. Found: C, 63.24; H, 4.87; N, 14.80. FD-MS: m/e 378; NMR (DMSO-d6): delta 2.975 (t, 2H), 4.235 (t, 2H), 4.418 (s, 2H), 6.928 (d, 2h), 7.151 (d, 2hO, 7.488-7.504 (m, 3H), 7.926-7.951 (m, 2H), 10.2 (br.s, 1H), 10.9 (br.s, 1H).

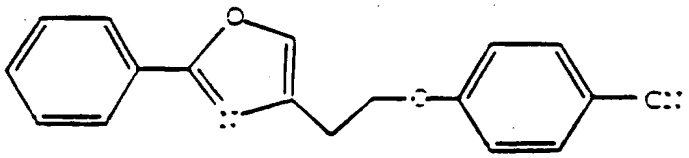
Example 18

Preparation of:
1-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,3-diazolidin-2,4,5-trione.



Part A

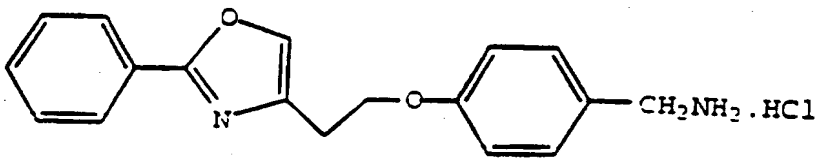
Preparation of:



To a 12.89 g of 60% dispersion of NaH in mineral oil, washed three times with hexanes, was added 100 mL of anhydrous DMF. The stirred suspension was cooled to 10°C and a solution of 52.1 g of alcohol from Example 9A Part A in 150 mL of anhydrous DMF was added dropwise. One hour after the completion of the addition, a solution of 37.59 g of para-fluoro-benzonitrile in 100 mL of anhydrous DMF (dimethylformamide) was added slowly while keeping the reaction mixture at 15-20°C. The reaction temperature was increased to 40°C while the mixture stirred for 4 hours. After the third hour, an additional 1.05 g of 60% NaH dispersion was added. The reaction was allowed to stay at 25°C for 16 hours and was then diluted slowly with 880 mL of H_2O. The precipitate which formed was filtered, washed with 1 L of H_2O followed by 1 L of hexanes and dried to give 71.8 g of 4-(2-(2-phenyl-4-oxazolyl)ethoxy)benzonitrile (90%, mp 114.6-115°C).

Part B

Preparation of:

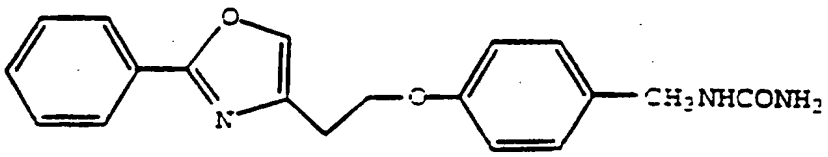


A solution of 12.34 g of nitrile from Example 18 Part A in 80 mL of anhydrous THF was added to a stirred suspension of 1.70 g of lithium aluminum hydride in 110 mL of anhydrous THF cooled to 10°C over a 5 min period. Stirring at 10°C was continued for 1.5 hours and then at 25°C for 20 hours. The reaction mixture was decomposed by the sequential addition of 1.8 mL of H_2O, 1.3 mL of 5N NaOH and 6.3 ml of H_2O. The slurry was filtered and the solid was washed with THF. The combined filtrates were evaporated and the residue was dissolved in 500 mL of EtOAc. The solution was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and filtered. Evaporation of the solvent left 12.4 g of amine which was taken up in MeOH and converted to the HCl salt by treatment with a solution of HCl in Et_2O. The residue, after evaporation of the volatiles, was crystallized from a mixture of 60 mL of MeOH and 350 mL of EtOAc. After filtration, the solid was washed with EtOAc and dried to give 11.4 g of 4-[(2-(2-phenyl-4-oxazolyl)ethoxy)-benzene]methyl amine hydrochloride (90%, mp 198-206°C).

FD-MS: m/e 294; NMR (DMSO-d6): delta 2.963 (t, 2H), 3.879 (d, 2H), 4.239 (t, 2H), 6.958 (d, 2H), 7.360 (d, 2H), 7.468-7.488 (m, 3H), 7.905-7.930 (m, 2H), 7.997 (s, 1h), 8.271 (br.s, 3H).

Part C

Preparation of:



A mixture of 10.3 g of free amine of example 18 Part B, 120 mL of H_2O, 120 mL of MeOH and 7.0 mL of 5N HCl was stirred until the amine dissolved and 2.27 g of sodium cyanate was added. The reaction mixture was warmed to 50°C and then allowed to cool to 25°C. After 2.5 hours, the mixture was cooled in an ice bath and filtered. The solid was washed with H_2O and recrystallized from 250 mL of EtOH and 350 mL of H_2O to give 6.05 g of N-4-(2-(2-phenyl-4-oxazolyl)ethoxy)-benzenemethyl urea (61%, mp 191-196°C).

Elemental analysis for $C_{19}H_{19}N_3O_3$, Calcd.: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.59; H, 5.75; N, 12.16. FD-MS: m/e 337; NMR (DMSO-d6): delta 2.946 (t, 2H), 4.040 (d, 2h), 4.195 (t, 2H), 5.425 (s, 2H), 6.261 (t, 1H), 6.862 (d, 2H), 7.113 (d, 2HO, 7.464-7.485 (m, 3H), 7.902-7.932 (m, 2h), 7.986 (s, 1H).

Part D

Preparation of Example 18:

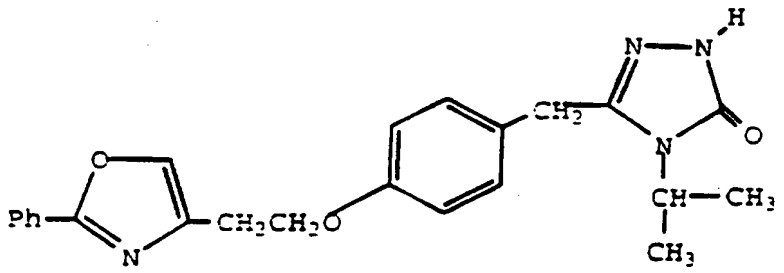
To a solution of 0.38 g of Na in 100 mL of anhydrous MeOH at 0°C was added 4.5 g of the substituted urea of Example 18 Part C. After several minutes of stirring, 2.0 mL of diethyl oxalate was added. The cooling bath was removed and the reaction mixture was stirred for four days. After the addition of 3 mL of 3N HCl and H_2O, the mixture was filtered. The solid was washed with H_2O and recrystallized

form 65 mL of THF and 75 mL of H_2O to give 3.28 g of 1-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)-phenyl)methyl]1,3-diazolidin-2,4,5-5-trione (63%, mp 217-223°C).

Elemental analysis for $C_{21}H_{17}N_3O_5$, Calcd.: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.72; H, 4.52; N, 10.59. NMR (DMSO-d6): delta 2.946 (t, 2H), 4.216 (t, 2H), 4.510 (d, 2H), 6.882 (d, 2HO, 7.209 (d, 2H), 7.464-7.482 (m, 3H), 7.898-7.927 (m, 2H), 7.984 (s, 1H), 12.011 (s, 1H).

Example 19

Preparation of:
4-Isopropyl-5-[4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl] 1,2,4-triazolin-3-one.



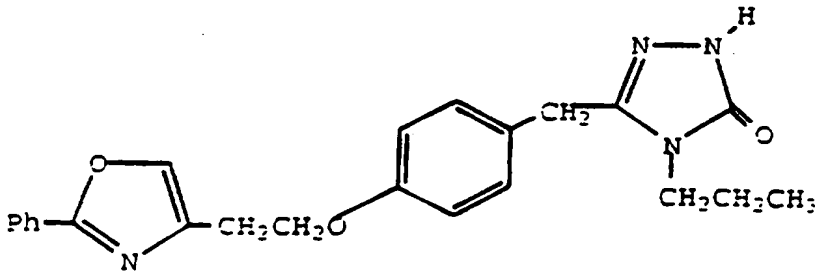
A suspension of 4.0 gm of the intermediate prepared as in Example 1 Part B was suspended in 30 mL of THF, treated with 1.3 g of iso-propyl isocyanate and refluxed for 2 hours. The mixture was cooled, diluted with Et_2O and filtered. The white solid (3.1g) was collected, washed with Et_2O and added to a solution prepared from 4.19 gm of 85% KOH and 100 mL of MeOH. The resulting solution was heated to reflux for 7 days, at which time TLC showed complete consumption of starting material. The cooled solution was acidified with 1N HCl and the resulting precipitate collected by filtration. Purification was effected by sequential chromatography on

silica gel columns, eluting with EtOAc and 30:1 $CHCl_3$/MeOH, respectively to provide 1.5 g (52%) of 4-isopropyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl] 1,2,4-triazolin-3-one as white needles, mp 140-143°C.

Anal. Cal. for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.31; H, 6.10; N, 13.88. IR: 1685cm^{-1}. MS: m/e 404. NMR: 1.3 (d, 2H), 3.09 (t, 2H), 3.84 (s, 2H), 4.01 (septet, 1H), 4.28 (t, 2H), 6.9 (d, 2H), 7.12 (m, 3H), 7.57 (s, 1H), 8.03 (m, 2H), 9.35 (s, 1H, exchanges with D_2O).

Example 20

Preparation of:
4-n-Propyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]1,2,4-triazolin-3-one.



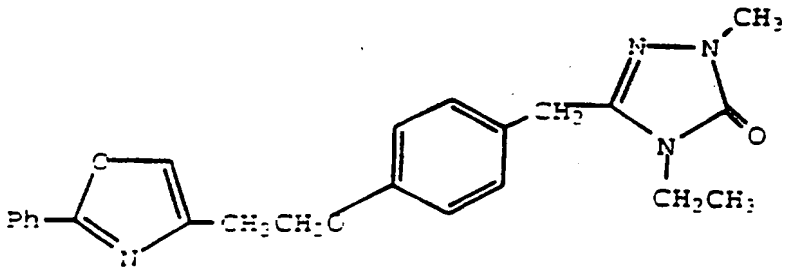
A suspension of 3.0 gm of the intermediate prepared as in Example 1 Part B was suspended in 30 mL of THF, treated with 1.01 g of n-propyl isocyanate and refluxed for 2 hours. The mixture was cooled, diluted with Et_2O and filtered. The white solid (3.3 g) was collected, washed with Et_2O and added to a solution prepared from 4.38 gm of 85% KOH and 100 mL of MeOH. The resulting solution was heated to reflux for 48 hours, at which time TLC showed complete consumption of starting material. The cooled solution was acidified with 1N HCl and the resulting precipitate collected by filtration.

Purification was effected by chromatography on silica gel, eluting with $CHCl_3$ to provide 2.3 g (73%) of 4-n-propyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-one as white needles, mp 131-132°C.

Anal. Cal. for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.26; H, 6.13; N, 13.87. IR: 1694cm^{-1}. MS: m/e 404. NMR: 0.72 (t, 3H), 1.31 (m, 2H), 3.0 (t, 2H), 3.34 (m, 4H), 3.84 (s, 2H), 4.25 (t, 2H), 6.92 (d, 2H), 7.17 (d, 2H), 7.54 (m, 3H), 7.97 (m, 2H), 8.02 (s, 1H), 11.45 (s, 1H), exchanges with D_2O).

Example 21

Preparation of:
2-Methyl-4-ethyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-one.



A stirred solution of 1.0 gm of the intermediate prepared in Example 2, Part A in 75 mL of DMF under N_2 was treated in one portion with .06 gm of 60% of NaH/oil and the resulting mixture allowed to react for 15 minutes. After addition of 0.54 gm of CH_3I, the mixture was kept at ambient temperature for 1 hour, poured onto ice and extracted with 100 mL EtOAc. The EtOAc solution was washed with H_2O, dried with Na_2SO_4 and evaporated. The solid residue was chromatographed over silica (elution with 2% MeOH in $CHCl_3$)

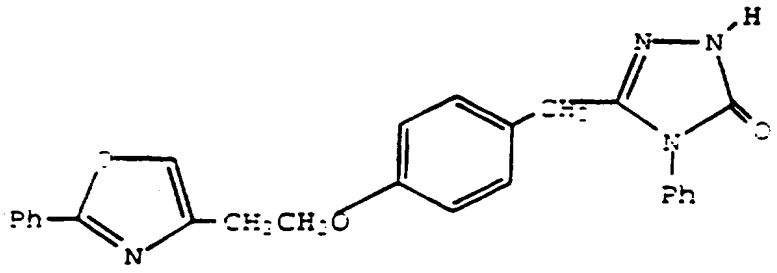
to provide 0.7 gm (67%) of 2-methyl-4-ethyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-one as colorless needles, mp 128-130°C.

Anal.: Cal. for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.09; H,m 5.98; N, 14.00. Ms: m/e 404. IR: 1690cm^{-1}. NMR: delta 1.0 (t, 3H), 3.07 (t, 2H), 3.25 (s, 3H), 3.3 (q, 2H), 4.26 (t, 2H), 6.88) d, 2h), 7.12 (d, 2H), 7.43 (m, 3H), 7.55 (s, 1H), 8.02 (m, 2H).

Example 21A

This Example prepares a compound outside the scope of the invention (contrast to compound prepared in Example 21, supra).

Preparation of:
4-Phenyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-methyl]1,2,4-triazolin-3-one.



A suspension of 3.0 gm of the intermediate prepared as in Example 1 Part B was suspended in 30 mL of THF, treated with 1.4 g of phenyl isocyanate and refluxed for 2 hours. The mixture was cooled, diluted with Et_2O and filtered. The white solid (2.8 g) was collected, washed with Et_2O and added to a solution prepared from 3.87 gm of 85% KOH and 100 mL of MeOH. The resulting solution was heated to reflux for 7

days, at which time TLC showed complete consumption of starting material. The cooled solution was acidified with 1N HCl and the resulting precipitate collected by filtration. Purification was effected by recrystallization from MeOH to provide 1.3 g (43%) of product as white needles, mp 179-181°C.

Anal. Cal. for $C_{26}H_{22}N_4O_3$: C, 71.22; H, 5.06; N, 12.78. Found: C, 71.11; H, 5.14; N, 12.97. IR: 1719cm^{-1}. MS: m/e 438. NMR: 2.97 (t, 2H), 3.73 (s, 2H), 4.19 (t, 2H), 6.78 (d, 2h), 6.85 (d, 2h), 7.22 (dd, 2H), 7.44 (m, 3H), 7.83 (m, 3H), 7.97 (m, 2H), 8.02 (s, 1h), 11.71 (s, 1H, exchanges with D$_2$O).

Testing Methods and Results

Compounds were tested for antihyperglycemic activity according to the protocol described in A.M. Gill and T.T. Yen, "Effects of Ciglitazone on Endogenous Plasma Islet Amyloid Polypeptide and Insulin Sensitivity in Obese-Diabetic Viable Yellow Mice" Life Sciences 48, 703-710 (1991). The mice used in these tests were obese-diabetic viable yellow mice form the inbred Lilly colony. They were housed in transparent plastic cages with bedding. Purina Formula Chow 5008 (product of Purina Mills Inc., 717 South Hickory St., Fond Du Lac, WI 54935-5517 USA) and water were available ad libitum. The ambient temperature of the animal room was 25°C and lights were on from 0600 to 1800.

To study the effects of the candidate compounds, twelve male obese-diabetic viable yellow (VY) mice were divided into two groups for each candidate compound. One group was fed mesh or repelletized Purina 5008 Chow and one group was fed the same chow (mammal food) containing the indicated amount of candidate compound as set forth below in

the Table. Body weight and food consumption were monitored and blood samples collected before the experiment was initiated and after 14 days of treatment. In the Table, the blood glucose levels of mice given the test compounds are reported as a percentage of the initial value as compared to untreated controls on day 14 of treatment. Reductions of the initial values by less than 20% are regarded as inactive. The dose is the percent of compound incorporated into the feed (mesh or repelletized). The corresponding data for ciglitazone are included for comparison.

TABLE

Example No.	Dose	BG%
1	.05	46%
2	.03	43%
3	.03	59
4	.05	49.5%
5	.03	27.4%
6	.05	39.5%
7	.03	33%
8	.03	70.5%
8A*	.03	97.6%
9	.03	55%
9A*	.05	82%
10	.05	46.1%
11	.05	51%
11A*	.05	109%
12	.03	43%
13	.03	40.7%
14	.05	34.7%
15	.03	40%
16	.03	47%
17	.05	41.8%
18	.03	57%
19	.03	54.4%
20	.03	38.2%
21	.03	53%
21A*	.03	99.5%
Ciglitazone**	0.1	64%

* are comparative Examples to show criticality of structure

** control experiment

We claim:

1. An antihyperglycemic compound selected from the group consisting of C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 positions of the pentacycloazole ring and N-alkyl-substituted pentacycloazole pharmacophore containing nitrogen or other hetero atoms in positions selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 1 position of the pentacycloazole ring.

2. The compound of Claim 1, wherein the antihyperglycemic compound is a C-substituted pentacycloazole pharmacophore.

3. The compound of Claim 2, wherein the C-substituted pentacycloazole is a 2,3,5-triazole.

4. The compound of Claim 2, wherein the C-substituted pentacycloazole is a 2,3-diazole.

5. The compound of Claim 2, wherein the C-substituted pentacycloazole is a 2,5-diazole.

6. The compound of Claim 2, wherein the C-substituted pentacycloazole is a 1,3,4-oxathiazolin-5-one.

7. The compound of Claim 2, wherein the C-substituted pentacycloazole is a 1,2,4-thiodiazolin-5-one.

8. The compound of Claim 1, wherein the antihyperglycemic compound is a N-alkyl-substituted pentacycloazole pharmacophore.

9. A C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 positions of the pentacycloazole ring having the structure $Ar-(G)_{n-1}-(CH_2)_{m-1}-CH_2Z$ wherein Z is the C-substituted pentacycloazole ring containing heteroatoms in the 2, 3 and 5 positions of the pentacycloazole ring, G is oxygen or sulfur, m and n are whole numbers ranging from 1 to 2 and Ar is a suitable aromatic system.

10. A C-substituted pentacycloazole pharmacophore of Claim 9, where Ar has the structure

$$Y-(CH_2)_p-(G')-Ar'-$$

wherein Ar' is a divalent arylene moiety, G' is oxygen or sulfur, Y is selected from the group consisting of substituted or unsubstituted aryl, cycloalkyl and heterocyclic and p is a number from 1 to 6.

11. The C-substituted pentacycloazole of Claim 10, wherein p is 1, G' is oxygen, Ar' is p-phenylene, m and n are 1 and Y is 2-phenyl-4-oxazolyl.

12. The compound of Claim 11, wherein C-substituted pentacycloazole is a 2,3,5-triazole.

13. The compound of Claim 11, wherein C-substituted pentacycloazole is a 2,3-diazole.

14. The compound of Claim 11, wherein C-substituted pentacycloazole is a 2,5-diazole.

15. The compound of Claim 11, wherein C-substituted pentacycloazole is a 1,3,4-oxathiazolin-5-one

16. The compound of Claim 11, wherein C-substituted pentacycloazole is a 1,2,4-thiadiazolin-5-one.

17. An N-alkyl-substituted pentacycloazole pharmacophore containing nitrogen atoms in positions selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3-position of the pentacycloazole ring having the structure Ar-(G)$_{n-1}$-(CH$_2$)$_{m-1}$-CH$_2$2 wherein 2 is the N-substituted pentacycloazole ring, G is oxygen or sulfur, m and n are whole numbers ranging from 1 to 2 and Ar is a suitable aromatic system.

18. The N-substituted pentacycloazole pharmacophore of Claim 17, wherein Ar has the structure Y-(CH$_2$)$_p$-(G')-Ar'- wherein Ar' is a divalent arylene moiety, G' is oxygen or sulfur, Y is selected for the group consisting of substituted or unsubstituted aryl, cycloalkyl and heterocyclic and p is a number from 1 to 6.

19. The N-substituted pentacycloazole of Claim 18, wherein p is 2, G' is oxygen, Ar' is p-phenylene, m and n are 1 and Y is 2-phenyl-4-oxazolyl.

20. A compound selected from the group consisting of (A) thru (T);

(A) 4-Methyl-5-[4-([2-(2-phenyl-4-oxazolyl)ethoxy]phenyl)methyl]1,2,4-triazolin-3-one;
(B) 4-n-Butyl-5-[4-([2-(2-phenyl-4-oxazolyl)ethoxy]phenyl)methyl]1,2,4-triazolin-3-one;

(C) 4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-thione;
(D) 1(3)H-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-thione;
(E) 3-Methylthio-4-methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazoline;
(F) 4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)2-oxaethyl]1,2,4-triazolin-3-one;
(G) 4-Methyl-5-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-2-ethyl]1,2,4-triazolin-3-one;
(H) 4-Methyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)-2-ethyl]1,2,4-triazolin-3-thione;
(I) 5-[4-((2-(2-phenyl-4-oxazolyl)-ethoxy)phenyl)methyl]1,2,4-oxadiazolin-3-thione;
(J) 5-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-one;
(K) 5-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]2,3,4-oxadiazolin-2-one;
(L) 3-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-oxadiazolin-5-one;
(M) 5-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,3,4-oxathiazolin-2-one;
(N) 3-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-thiadiazolin-5-one;
(O) 1-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolidin-3,5-dione;
(P) 1-((4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,3-diazolidin-2,4,5-trione;
(Q) 4-Isopropyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl] 1,2,4-triazolin-3-one;
(R) 4-n-Propyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-one; and

(S) 2-Methyl-4-ethyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-one; and
(T) 4-Ethyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl] 1,2,4-triazolin-3-one.

21. The compound (T) of Claim 20: 4-Ethyl-5-[4-((2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl] 1,2,4-triazolin-3-one.

22. An antihyperglycemic composition comprising a pharmaceutically acceptable carrier, diluent or excipient and an effective amount of an antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2, 3 and 5 position of the pentacycloazole ring and N-substituted pentacycloazole pharmacophore containing nitrogen atoms in positions selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3 position of the pentacycloazole ring.

23. The composition of Claim 22, wherein the antihyperglycemic compound is a C-substituted pentacycloazole pharmacophore.

24. The composition of Claim 23, wherein the C-substituted pentacycloazole is a 2,3,5-triazole.

25. The composition of Claim 22, wherein the antihyperglycemic compound comprises from 1 to 99 weight percent of the composition.

26. A method of reducing the hyperglycemia associated with non-insulin dependent diabetes mellitus which

method comprises orally administering to a mammal a therapeutic dose of a antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 position of the pentacycloazole ring and N-substituted pentacycloazole pharmacophore containing nitrogen atoms in position selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring the 3 position of the pentacycloazole ring.

27. The process of Claim 26, wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14100

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/42; C07D 263/30
US CL :514/374, 548/235, 237, 239
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/374, 548/235, 237, 239; A61K 31/420

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 5,334,604 (GOLDSTEIN et al.) 02 August 1994, see abstract, example 2 (column 9, lines 14-column 10, line 3)	1, 2, 8, 9-11, 17-19, 22-23, 25-27 --- 3-7, 12-14, 21, 26
Y	US, A, 4,763,956 (SCHNUR) 28 June 1988, see claims 1, 4, 5.	1, 2, 8
X	US, A, 5,066,662 (HOBBS et al.) 19 November 1991, see abstract, column 3, lines 10-42 and 61; column 7, lines 7, 8, 11, 12, 25-32, 51-63; column 8, lines 13-27; claims 1-5.	1, 2, 4-6, 8-10, 14, 15, 17, 22-23, 25
X	US, A, 5,185,353 (TURNBULL et al.) 09 February 1993. See column 2, table 2, compounds 26, 27; column 1, lines 32-33.	1, 28, 22-23, 25

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
28 DECEMBER 1996

Date of mailing of the international search report
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14100

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,254,576 (ROMINE et al.) 19 October 1993, see entire document.	1-27
X	US, A, 5,239,080 (SOHDA et al.) 24 August 1993. See column 2, lines 55-57, 62-63, 66-67 and column 1, lines 45-47.	1-5, 9-14, 22-26
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Y		8, 17-21

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14100

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11, 17-19, 22-27 (part of each), and 12-14, 21

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14100

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-11, 17-19, and 22-27 (part of each), 12-14, and 21, drawn to pentacyclazoles (PCA) where one is oxazole and the other (if present) is 1,2,3-triazole or 1,2,4-triazole.

Group II, claim(s) 1-11, 17-20, and 22-27 (part of each), drawn to one PCA is oxathiazoline.

Group III, claim(s) 1-11, 17-19, and 22-27 (part of each), drawn to one of the PCA's is 1,2,3 thiadiazole.

Group IV, claim(s) 1-11, 17-20, and 22-27 (part of each), 15, drawn to one of the PCA's is 1,2,4 thiadiazole and the other isn't II.

Group V, claim(s) 1-11, 17-20, and 22-27 (part of each), drawn to one PCA is 1,2,4 oxadiazoles and the other isn't II-IV.

Group VI, claims 1-11, 17-19 (part of each), drawn to one of the PCA's is 1,2,5 thiadiazoles and the other isn't II-V.

Group VII, claims 1-11, 17-20, and 22-27 (part of each), drawn to one of the PCA's is 1,3,4 thiadiazoles and the other isn't II-VI.

Group VIII, claims 1-11, 17-20, and 22-27 (part of each), and 14, drawn to one of the PCA's is 1,3,4 oxadiazoles and the other is not II-VII.

Group IX, claims 1-11, 17-19, 22-27 (part of each), drawn to one of the PCA's is thiazole and the other isn't II-VIII.Group X, claims 1-11, 17-19, and 22-27 (part of each), drawn to PCA is 1,2,3 triazole and not in II-IX.

Group XI, claims 1-11, 17-19, and 22-27 (part of each), drawn to PCA is 1,2,4 triazole and not in II-X.

Group XII, claims 1-11, 17-19, and 22-27 (part of each), drawn to PCA is 1,3 diazole (imidazoles) and not in II to XI.

Group XIII, claims 1-11, 17-19, and 22-27 (part of each), drawn to PCA is 1,2 diazole (pyrazole) and not in II to XIII.

Group XIV, claims 1-11, 17-19, and 22-27 (part of each), drawn to PCA's not provided above.

The inventions listed as Groups I-XIV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They do not have a common "special technical feature" not shared with Goldstein (see abstract) or Sohda. Indeed some claims (eg. 1) are so obscure it appeared there is no common technical feature, i.e. either drawn a C substituted PCA or a N alkyl substituted PCA, not having a technical feature at all common to claim 1. The heteroatoms aren't even recited, other than N in the N alkyl substituted PCA. The claim is literally impossible of complete search in the PTO search files.